

ORGANIC CHEMISTRY

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A. F. HOLLEMAN

LL. D., D. Sc., F.R.S.E.

ORGANIC CHEMISTRY

by

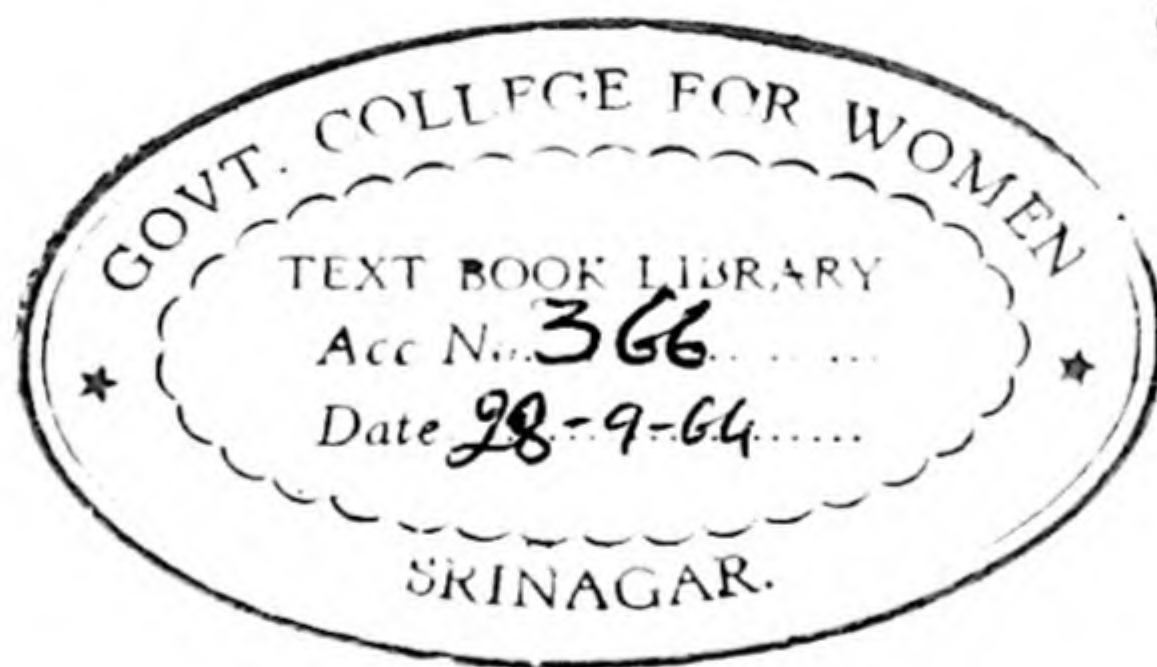
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PREFACE

This book is a continuation of the *Textbook of Organic Chemistry* by A. F. HOLLEMAN, the last English edition of which appeared in 1930.

Since that time, the adaptation of this book has been taken over by the undersigned, special care being taken that the original character of the book should be retained, *i.e.* that the subject matter should be treated not only from the standpoint of the organic chemical theory of structure but also from a physico-chemical point of view.

This book is not intended only for students who have chosen chemistry as their main subject, but also for students of medicine and biology. It should render good service to biologists and medical students, who may wish to obtain an insight into the structure of the substances with which they come into contact in the course of their profession.

The important groups of aliphatic, aromatic, alicyclic and heterocyclic compounds are systematically treated in succession, in such a way, that not only can an insight be obtained into the results and problems of organic chemistry, but also into the historical development of this branch of chemistry.

The recent development of the chemistry of acetylene (vinylacetylene, chloroprene, the preparation of butadiene) is dealt with in the section on aliphatic hydrocarbons; cyclo-octatetraene is discussed in the chapter on benzene.

The calculation of the bonding energy values of the atoms is discussed as well as the direct determination of heats of hydrogenation. The electronic configuration of the carbon-carbon double-bond is dealt with in the structure of the alkenes.

In the discussion of *cis-trans* isomerism, the configuration of crotonic acid is considered as well as the mechanism of the photochemical conversion of maleic acid into fumaric acid.

In addition, the following subjects, amongst others, are discussed: investigation of the CANNIZZARO reaction with the aid of deuterium, the mechanism of the formation and hydrolysis of esters with the help of the oxygen isotope ^{18}O and the mechanism of the WALDEN inversion with radioactive iodine.

The arrangement of molecules in mono-molecular layers is discussed with

the fatty acids and when dealing with fats, the synthesis of glycerides is discussed; the detergent action of soap is also dealt with.

The determination of the configuration of optically active compounds is treated in the chapter on stereo-chemistry, so that the determination of the configuration of the mono-saccharides can be seen as a special case.

Electronic formulae are used in the stereo-chemistry of nitrogen and sulphur compounds and the resolution of a tertiary nitrogenous base into optically active components is examined.

For the benefit of readers interested in biochemistry, detailed attention has been given to the most important groups of natural products, such as sugars, starch, cellulose, proteins, terpenes, carotenoids, sterols, vitamins, hormones and alkaloids. Thus in the section on sugars, the biochemical synthesis of sucrose and the determination of the configuration of glucosamine are mentioned. The chapter on starch is written up, in collaboration with Prof. N. P. BADENHUIZEN (Johannesburg, South Africa), in accordance with the most recent biochemical ideas; the biochemical synthesis of starch is discussed. Alcoholic fermentation is treated in broad outline.

In the chapters on amino-acids and proteins, the most recent investigations of ROSE on essential amino-acids, as well as those of KÖGL on *d*-amino-acids from cancerous tumours, and the polyamides of the Nylon type, all find a place.

The idea of mesomerism is discussed in connection with the structure of benzene; in aromatic substitution, nitration and halogenation are discussed as examples of electrophylic substitution. The temperature effect in halogenation is also discussed as well as the mutual conversion of the bromonaphthalenes.

A separate chapter is devoted to electrolytic reduction, especially of aromatic nitro-compounds.

In the treatment of synthetic dyestuffs, a chapter is devoted to the relationship between colour and structure and the most important vegetable colouring matters, including the anthocyanins and flavones, alizarin, indigo, etc., are discussed. An example is also given of a phthalocyanine pigment.

The terpenes and camphors are dealt with in the chapter on cyclanes; synthetic rubbers are treated along with caoutchouc.

In addition to a chapter dealing with carotenoids, there is a chapter devoted to vitamins and hormones, including pantothenic acid, vitamin-B₁₂ and corticosterone. The remaining vitamins and hormones are discussed in the appropriate places, where they belong, according to their structure. Various antibiotics of importance in medicine are discussed, including the sulphapyridines and the penicillins as derivatives of thiazole. Amongst the alkaloids, the constitution of strychnine is discussed on the basis of

the structural formula, which has been established by chemical and röntgenographical investigations.

At the end of the book is given a short introduction on how to consult the literature on organic chemistry, which we hope will be a welcome directive for beginners in this frequently much neglected subject.

During the preparation of this book I have received much useful advice from numerous colleagues.

The writing of this textbook has been greatly facilitated by the co-operation of my wife, A. J. P. WIBAUT-VAN GASTEL, D. Sc. (Amsterdam), both in the study of the literature and in the composition of the manuscript and the Index. The translator acknowledges with many thanks the very useful service rendered by Mr. H. N. HADDOCK, B.Sc., F.R.I.C., from I.C.I., Manchester, who kindly read through the whole of the typescript of the translation.

Amsterdam, February, 1951

J. P. WIBAUT

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GENERAL ASPECTS OF ORGANIC CHEMISTRY

CHAPTER 1

INTRODUCTION

1. The name *organic chemistry* for that part of chemistry, which may be defined at present as the chemistry of carbon compounds, is best understood from the historical development of this science. Originally, by organic chemistry was meant the chemical examination of substances derived from the vegetable and animal kingdoms. A few substances, which we now include amongst organic compounds, such as ethyl alcohol and acetic acid, were already known in ancient times, but these substances were first obtained in a pure state only many centuries later. Also, some naturally occurring dyestuffs, like indigo and the dyestuff from certain species of shell-fish (the Purple of the Ancients), were already known before our era. Many vegetable or animal materials were used in daily life—our foodstuffs and clothing materials—in commerce and the arts and for pharmaceutical purposes.

Gradually men learned how to separate definite substances from vegetable and animal products: benzoic and succinic acids were found in the 16th century. Beet-sugar was discovered in 1747 by MARGRAF, who found that it was the same substance as cane-sugar, which had already been known for a long period. In the second half of the 18th century C. W. SCHEELE (1742–1786) isolated a number of acids occurring in plants, such as tartaric acid, oxalic acid, malic acid, citric acid and gallic acid. The isolation of urea from urine was described as early as 1732 by H. BOERHAVE (1668–1738). At the beginning of the 19th century the important investigations of CHEVREUL (1786–1889) appeared on the chemical composition of fats, in which a number of fatty acids were described.

In time, chemistry began to develop as an exact science; the analytical composition of substances was systematically determined. A. L. LAVOISIER (1743–1794) had already established, that many substances from the vegetable and animal kingdoms were built up from a limited number of elements only, namely, carbon, hydrogen, oxygen and sometimes also nitrogen, as distinct from substances of the mineral kingdom, among which a greater number of elements were encountered. The examination of plant and animal substances was at first limited to analysis. The composition

of such substances and of the decomposition products which could be obtained from them by various means, especially by heating, was determined.

Even before the beginning of the 19th century men had learned how to prepare a number of inorganic salts, bases and acids in the laboratory and also how to obtain them starting from the elements. It appeared that it would be much more difficult, however, to build up from simpler constituents, the substances, which men had learned to isolate from vegetable or animal material.

Actually, for this purpose, a profound knowledge of the complicated composition and the peculiar structure, which characterise many of the substances occurring in living nature, was necessary. The foundations on which this knowledge could be based was only obtained during the first half of the 19th century after a great deal of experimental work.

It was, however, clear that the formation of chemical compounds in the living organism takes place under quite different conditions from those which are used in the preparation of inorganic substances in the laboratory. Indeed chemical processes take place in the living organism at ordinary or slightly elevated temperatures: powerful reagents like strong acids or bases, chlorine, sodium or phosphorus in the free state, are completely out of the question. Very complicated compounds such as sugars, fats, proteins and many others, are produced by unknown ways in the plant, which has only carbonic acid, water, ammonia and mineral salts available to it as starting materials. At the same time the vital processes are characterised by growth and propagation and so differ entirely from the changes in inorganic nature.

Thus the idea occurred to naturalists of previous centuries—held mostly in a vague and mystical form—that in the living organism a special influence was active, which could not be more closely defined and was identified as “vis vitalis” or as “vital force” and initiated all living processes and maintained them.

From this mode of thought arose the supposition, that the chemical substances themselves occurring in the living organism, could be formed only by intervention of this “vital force”. If this was correct, naturally it was not possible to obtain vegetable or animal substances from dead inorganic materials.

This mode of thought was still predominant during the first half of the 19th century, so that it was held to be impossible to construct a complicated organic compound from its decomposition products and a fortiori to obtain even a simple organic compound from the elements. SCHEELE had already obtained potassium cyanide in 1783 by heating a mixture of potash and

powdered graphite with sal-ammoniac. Since however, potassium cyanide does not occur in the living organism—the formation of hydrocyanic acid as a fission product of some vegetable substances was only discovered much later—this synthesis of potassium cyanide from inorganic materials was of no significance for the teaching of the vital force.

In 1824 F. WÖHLER obtained oxalic acid from cyanogen gas and in 1828 the same investigator prepared urea from ammonium sulphate and potassium cyanate. Thus here two substances, which are also formed in the living organism, were obtained by synthesis in the laboratory. However, this discovery did not result immediately in the abandonment of the vital force theory. J. BERZELIUS still wrote in 1831, that there was little hope of ever being able to prepare organic substances artificially. So at this time confusion reigned as regards the various components of organisms, such as fibres, muscles, cells in general and the actual organic compounds, from which these components were constructed.

Gradually other syntheses became known, which could rank as methods of formation from the elements, such as that of acetic acid by KOLBE (1845) and those of ethyl alcohol, formic acid, ethylene and acetylene by M. BERTHELOT during the years 1855–1863.

It was M. BERTHELOT (1827–1907) especially, who demonstrated in a number of examples, that organic compounds could be obtained by synthesis from inorganic materials. In his famous book: “*La chimie organique fondée sur la synthèse*” it was proved on this basis that “organic” substances are produced under the influence of the same forces as inorganic compounds.

As a consequence of all these researches the notion of an unknown influence, a “vital force”, which should be necessary for the formation of organic substances, was completely abandoned.

Numerous discoveries made in the domain of organic chemistry during the first half of the 19th century, in connection with which the French investigators J. B. DUMAS (1800–1884), A. LAURENT (1807–1853), C. GERHARDT (1816–1856), the Germans J. LIEBIG (1803–1873), F. WÖHLER (1800–1882), E. MITSCHERLICH (1794–1863) and the Englishmen E. FRANKLAND (1825–1899) and A. WILLIAMSON (1824–1904) should be mentioned, gradually gave a much broader basis to this branch of science.

Men no longer limited themselves to the examination of products from the vegetable or animal kingdoms, but learned how to prepare numerous carbon compounds, which did not occur in living nature. The connection between various groups of compounds was found as a result of systematic investigation.

The principal difference between inorganic and organic had fallen down; organic chemistry was no longer only an analytical, but had become primarily

a synthetic science. The synthesis of organic substances from simpler components always made greater progress. At the present time many extremely complicated compounds, which occur in the plant or animal organism, are built up in the laboratory.

Organic chemistry thus became the chemistry of carbon compounds and the question may be asked why this portion of chemistry should be treated as a separate subject. One reason is, that the number of carbon compounds known at the present time is estimated to be not far from 1,000,000, that is more than 20 times as many as the number of compounds of all the other elements together.

There are, however, still other reasons making separate treatment desirable. The carbon compounds are characterised especially by peculiar properties, which are not apparent to the same extent in compounds of other elements. This will of course appear later on; nevertheless a word or two should be said about it in this introduction.

As regards its properties, the element carbon stands in between the typically electropositive and the typically electronegative elements, which is expressed in the position of carbon at the head of the fourth group of the periodic system. This element, which itself is electrically neutral in character, can form stable compounds both with hydrogen and metals and also with halogens, oxygen, sulphur and nitrogen. This already raises the possibility of the existence of a number of groups of carbon compounds.

Still another property of carbon atoms is manifested in compounds of this element, namely, that they can be joined together to form chains of a large number of atoms. This power of forming chains of atoms, which is not met to this extent with atoms of other elements, is the reason why the number of carbon compounds is so large.

While many inorganic substances, salts, bases and acids, are split up in aqueous solution or in the fused state into components with opposite electrical charge (ions), large classes of organic compounds are not ionised in solution or in the liquid state. In accordance with this is the fact that the velocity, with which reactions between carbon compounds take place, is usually small compared with that of reactions between ionogenic compounds, which so frequently occur in inorganic chemistry. It is clear that one must take into account this slow rate of reaction in the experimental investigation of organic-chemical reactions.

With the low reactivity of carbon compounds is connected a phenomenon, which is characteristic of this group of substances, namely, *isomerism*, by which is meant the occurrence of compounds having the same composition and molecular size, but differing from each other in properties. *Chemical structure theory*, which has been developed to take account of the existence

of isomeric compounds, is the most important part of the theoretical system of present day organic chemistry. From the nature of the case, it was necessary to discover experimental methods in order to be able to learn the properties of isomeric compounds. The occurrence of isomeric compounds is an exception in inorganic compounds.

We have seen that the name organic chemistry arises from its historical development. Yet this name is not of historical significance only. The examination of the chemical properties and of the mutual relationship of the substances, which are brought forth by living agencies, is still always a pre-eminently important problem in the chemistry of carbon compounds, which may now therefore also be called organic chemistry.

CHAPTER 2

QUALITATIVE AND QUANTITATIVE ANALYSIS OF ORGANIC COMPOUNDS

2. It has already been mentioned above, that by far the greater proportion of organic compounds are built up from a small number of elements (LAVOISIER, BERZELIUS). The hydrocarbons, which contain only carbon and hydrogen, form a large class of compounds; substances, which contain, besides carbon and hydrogen, also oxygen are even more numerous. A great number of compounds contain nitrogen as well as carbon and hydrogen and in very many of these, oxygen also occurs along with the three elements. Further, carbon compounds are known of practically all the elements with the exception of the noble gases. Among the elements from which compounds from the animal and vegetable kingdoms are constructed, the most important are carbon, hydrogen, oxygen and nitrogen. Phosphorus and sulphur also occur in a number of these compounds.

Further, organic compounds from plants and animals are known containing magnesium, iron, copper or iodine; calcium and potassium occur in the form of salts of organic acids.

The *qualitative analysis* of organic compounds, the aim of which therefore is to discover what kinds of atoms occur therein, can be carried out by oxidation. In this way carbon itself is converted into carbon dioxide, which can be detected with lime-water; hydrogen becomes water, nitrogen escapes as such; sulphur and phosphorus are oxidised to sulphuric acid and phosphoric acid, respectively. In the oxidation of organic metal compounds the metal is found in an easily recognisable form of combination, or in the elemental state if a noble metal is concerned.

This oxidation is carried out in different ways according to what element it is desired to detect. For testing for carbon, hydrogen and nitrogen use is very frequently made of copper oxide. For this purpose the two compounds are mixed and this mixture is heated in a tube sealed at one end. The oxygen of the copper oxide oxidises the carbon and the hydrogen. The nitrogen escapes as such; in order to demonstrate this element in this way, exactly the same method is followed as will be described more fully in the quantitative determination of nitrogen. If it is desired to test for halogens,

sulphur, phosphorus, etc., it is more practical to oxidise the substance under investigation with concentrated nitric acid.

In many organic substances the *nitrogen* can be converted into ammonia by heating with soda-lime or with concentrated sulphuric acid. Another method, which is very much used as a test for this element, was found by LASSAIGNE. It consists in heating the substance to be examined with a small piece of sodium in a narrow tube sealed at one end. If the compound contains nitrogen, sodium cyanide is formed, which gives a precipitate of Prussian Blue with a solution of ferrous sulphate and a little ferric chloride. The LASSAIGNE reaction does not succeed with substances, which already split off their nitrogen at slightly raised temperatures (*e.g.* diazo-compounds). Nitro-compounds also give only a weak reaction in this test.

Halogens may be tested for by heating the substance with quicklime; calcium halide is produced. A very sensitive method consists in heating a little of the compound with copper oxide in a non-luminous flame. Copper halide is produced, which volatilises in the flame with the production of a beautiful green colouration (BEILSTEIN test). These two methods can always be applied.

Sulphur can frequently be detected by heating the compound with a small piece of sodium in a narrow tube sealed at one end; in this case sodium sulphide is produced. The reaction mass is extracted with water and to the solution is added a solution of sodium nitroprusside [$\text{Na}_2\text{FeCy}_5(\text{NO}) + 2\text{aq}$]; the liquid assumes an intense violet colour.

The presence of *oxygen* in an organic compound can be made apparent only from a quantitative analyse, since no qualitative reaction is known, by which the presence of this element in organic compounds can be detected.

3. The *quantitative analysis* of organic compounds, the so-called *elementary analysis*, has the object of determining the ratios by weight, in which the elements are present in the compound. The oldest and most general method is the same in principle for all organic compounds and depends on oxidation.

Determination of carbon and hydrogen according to LIEBIG. The method used for this determination was recorded in principle by BERZELIUS and by GAY-LUSSAC and was simplified by LIEBIG and others.

The combustion takes place in a tube of difficultly fusible glass *ab* (Fig. 1) filled with a layer of coarsely granulated copper oxide, *ed*; this layer is kept in place on either side by rolls of copper gauze (*ce* and *df*), which are oxidised by heating in oxygen. A similar roll of oxidised copper gauze *gh* is placed at the end *a*, where the weighed quantity (0.1—0.2 g.) of substance to be analysed is found in a small porcelain boat *i*. The tube *ab* is placed in a

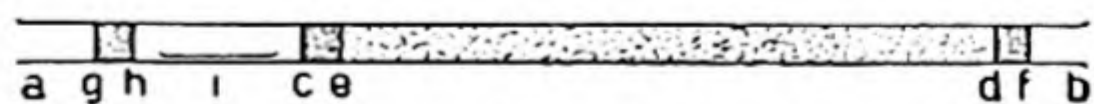


Fig. 1. Combustion tube for elementary analysis

combustion furnace *kl* (Fig. 2); during the combustion air or oxygen, which has previously been freed entirely from carbon dioxide and water vapour by means of the drying system *m*, (containing soda-lime and calcium chloride and to which a wash-bottle holding concentrated sulphuric acid is also attached) is passed through the tube at *a*. The gases issuing from the com-

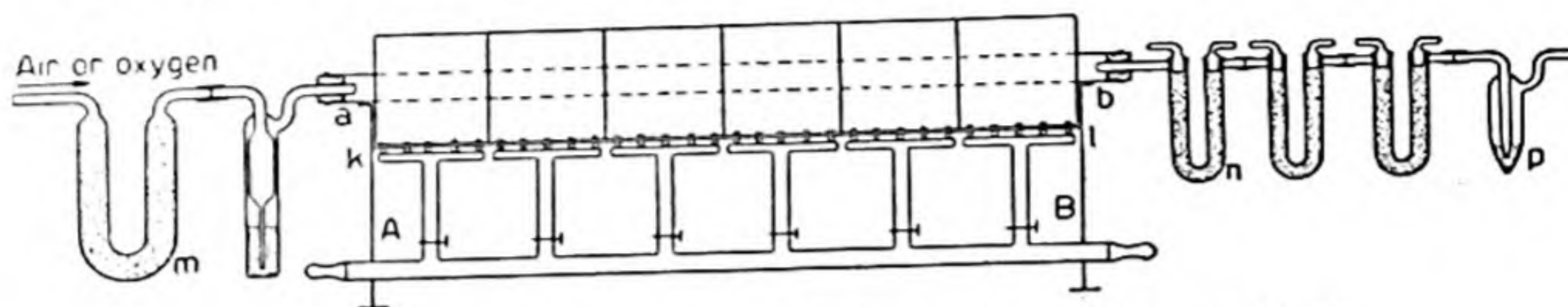


Fig. 2. Combustion furnace for elementary analysis

bustion tube at *b* flow first of all through a U-tube *n* filled with calcium chloride, in which the water formed is absorbed and then through three U-tubes containing soda-lime and calcium chloride (only two are shown in the figure), in which the carbon dioxide is taken up. After these U-tubes follows a small wash-bottle *p*, filled with sulphuric acid, which serves as a "bubble counter", in order to observe the speed of the gas stream. The combustion is carried out in such a way that the layer of copper oxide *ed* is first of all brought to a dull red heat and then by carefully heating the place where the boat is situated, the substance is slowly burnt first in a stream of air and finally in a stream of oxygen. The layer of heated copper oxide serves to oxidise gaseous decomposition products completely to carbon dioxide and water. From the increase in weight of the calcium chloride tube and the tubes containing soda-lime are found the quantities of water and carbon dioxide formed, from which are calculated the amounts of hydrogen and carbon, which were present in the weighed amount of substance.

If the substance contains nitrogen, a roll of clean copper gauze, which is gently heated during the estimation, is introduced into the combustion tube at *b*; the hot copper decomposes oxides of nitrogen, which may be formed in small quantities during the combustion and would otherwise be taken up in the soda-lime tubes. If the substance contains sulphur or halogens, a layer of lead chromate is introduced into the tube at *b* and is gently heated. In this way sulphur and halogens are fixed as lead sulphate and lead halides, respectively.

By the method described, the combustion of a few tenths of a gram of substance requires the use of a large and rather cumbrous apparatus. TER MEULEN and HESLINGA have worked out a method, which is much simpler in performance: manganese dioxide is used instead of copper oxide. Much

less of this is necessary so that a shorter combustion tube and a small combustion furnace can be used.

Determination of nitrogen by the method of DUMAS. For this purpose a similar apparatus to that for the determination of carbon and hydrogen according to LIEBIG is used. In place of purified air, carbon dioxide is led into the inlet of the combustion tube, the air in the tube being completely displaced before the beginning of the combustion. Instead of the U-tubes at the end of the combustion tube, there is placed a *nitrometer*, in which the nitrogen is collected over strong caustic potash solution, the gaseous combustion products, carbon dioxide and water, being absorbed in the alkali. At the end of the combustion, which is carried out in the same way as described for the determination of carbon and hydrogen (in this case also the combustion tube contains a roll of copper gauze, which is gently heated), all the nitrogen is driven over into the nitrometer by a stream of carbon dioxide. The nitrogen is eventually transferred into a measuring tube over water and the volume is measured at the same time as the temperature and the height of the barometer. The nitrogen content of the substance under investigation is calculated from these data.

Determination of nitrogen by the method of KJELDAHL. The nitrogen is split off quantitatively in the form of ammonia, from nitrogenous compounds in which the nitrogen is combined in the form of amino-, imino- or cyano-groups, if the organic substance is heated with concentrated sulphuric acid, which thereby acts as an oxidising agent and is converted into sulphurous acid. Sometimes another oxidising agent, such as manganese dioxide or potassium permanganate, is also added. A little mercury is added in addition, which passes into solution as the sulphate during the experiment and acts as an "oxygen carrier" by virtue of the conversion of mercuric sulphate into mercurous sulphate. The latter is reoxidised to mercuric sulphate by the sulphuric acid.

The reaction is carried out in a flask with a long neck, in which the mixture of sulphuric acid and a weighed amount of substance is heated; usually the mass blackens at first due to carbonisation and the liquid eventually becomes colourless again after a few hours' heating. The substance is then completely oxidised and the nitrogen is now present as ammonium sulphate. Therefore, after diluting the liquid and making alkaline, the ammonia can be distilled off and determined titrimetrically. This method, which is much simpler to carry out than the DUMAS method and gives equally accurate results, is of great importance for determining the nitrogen content of proteins and hence also for the analysis of foodstuffs and fodder. The KJELDAHL method cannot be used—at least in the form described here—with compounds in which the nitrogen is attached to oxygen, *e.g.* nitro- and

nitroso-compounds and similarly with azo-compounds and many compounds, in which the nitrogen is combined as a constituent of a nitrogenous ring system.

Determination of halogens by the method of CARIUS. In this method a weighed quantity of the substance under examination is introduced with a little fuming nitric acid and a crystal of silver nitrate into a sealed, thick-walled, glass tube; the latter is then heated in a thick-walled iron jacket for several hours at $180-300^{\circ}$. In this way the organic substance is completely oxidised and the halogen is converted into silver halide, which can be determined gravimetrically. This method is tedious but accurate in procedure, and can be applied to all substances containing halogen. The CARIUS method may also be used for the determination of sulphur, phosphorus and arsenic, the elements being oxidised to sulphuric acid, phosphoric acid and arsenic acid, respectively, which may then be determined by the usual methods of inorganic analysis.

Methods of TER MEULEN for the determination of sulphur, nitrogen, halogens and oxygen. While all the above-mentioned methods are based on *oxidation*, methods have been worked out by TER MEULEN, which depend on *reduction*; sulphur is converted into hydrogen sulphide, nitrogen into ammonia, halogens into hydrogen halides and oxygen into water. The *determination of nitrogen* by this method gives good results with all types of organic compounds no matter in what form the nitrogen is combined and in most cases is to be preferred to the method of DUMAS for its easy and simple method of procedure. The substance is heated with finely divided nickel in a stream of hydrogen at $250-400^{\circ}$, when all the nitrogen is converted into ammonia, which is collected and can then be determined by titration with acid.

For the *determination of sulphur* the substance is heated in a stream of hydrogen to $600-700^{\circ}$, the tube in this case being filled with platinised asbestos; the resultant hydrogen sulphide is determined iodometrically or as cadmium sulphide.

For the *determination of halogen* the substance is heated in a stream of hydrogen and gaseous ammonia. The combined halogen is then converted into the corresponding ammonium halide, which is deposited in the cooler part of the tube.

For the *determination of oxygen* the organic substance is heated in a stream of dry hydrogen; the decomposition products first of all come into contact with red hot platinised asbestos, by which they are decomposed in such a way that the combined oxygen in the organic compound is converted into carbon monoxide, carbon dioxide and water vapour. This mixture, mixed always with an excess of hydrogen, next comes into contact with a catalyst consisting of finely divided nickel on thorium oxide heated to 350° ,

by which the oxides of carbon are reduced and the combined oxygen is converted into water vapour (17). Thus in this way the oxygen combined in the organic compound is split off quantitatively as water, which is collected in a calcium chloride tube.

Before this method was known the percentage of oxygen could only be calculated by subtracting the sum of the percentages of all the other elements, which could be determined analytically, from 100. Thus all the errors of observation are accumulated in the oxygen figure. By means of the TER MEULEN method it is possible to test the accuracy of the analytical figures obtained also on compounds containing oxygen, since the sum of the percentage figures must be 100.

Example of the calculation of the percentage composition and of the empirical formula from the results of an analysis:

The following results were obtained on the analysis of a substance: 0.2169 g. of substance gave 0.0685 g. of water and 0.5170 g. of carbon dioxide. 0.2218 g. of substance gave 17.4 ccs. of nitrogen, measured over water at 6° C. at a barometric pressure of 762 mms.

Since 12 parts of carbon are present in 44 parts of carbon dioxide and 2 parts of hydrogen in 18 parts of water, the weight found for CO₂ must be multiplied by 12/44 = 3/11, to find the carbon content, and the weight found for water by 2/18 = 1/9, to obtain the hydrogen content. When this calculation is made, it appears, that 65.00 % of C and 3.51 % of H are present in the compound.

The weight of nitrogen is calculated as follows. Since it is saturated with water vapour, the vapour pressure of water vapour must be subtracted from the barometric pressure, in order to find the pressure of nitrogen. The vapour pressure amounts to 7.0 mms. at 6° C. Hence the pressure, under which the nitrogen stands, is 762 — 7 = 755 mms. The weight of 1 cc. of nitrogen at 0° and 760 mms. is 1.2562 mg.; 1 cc. of nitrogen at 755 mms. and 6° C. weighs in mgs.:

$$\frac{1.2562}{1 + 6 \times 0.00367} \cdot \frac{755}{760} = 1.22.$$

Hence the 17.4 ccs. of nitrogen found weigh $1.22 \times 17.4 = 21.23$ mg.; the nitrogen content is therefore 9.57 %.

The sum of these percentage figures for C, H and N is 78.08, from which it follows, that the oxygen content of the substance, which has been analysed, amounts to 21.92 %; thus from the analysis the percentage composition is:

C	65.00
H	3.51
N	9.57
O	21.92

These values, divided by the figure for the atomic weights of the respective elements, give:

C	H	N	O
5.42	3.51	0.68	1.37

These figures, divided by 0.68, in order to obtain as near as possible whole numbers, become:

C	H	N	O
7.9	5.1	1.0	2.0

figures which agree very closely with the formula $C_8H_5O_2N$. When the percentage composition is calculated for this formula, one finds:

C 65.31	H 3.40	N 9.52
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which agrees well with the analyse.

Elementary micro-analysis. In the methods discussed above 50–150 milligrams of substance are required for each analytical determination. In many researches, particularly on substances occurring in living organisms, only very small quantities of the compound to be examined can be isolated in a pure state, so that only a few milligrams are available for an analysis. PREGL has elaborated methods for elementary analysis, in which 3 to 10 mg. of substance will suffice for each determination. In principle these methods are carried out in the same way as the determinations of C and H by LIEBIG, the determination of N by DUMAS or of halogen by CARIUS. The apparatus is adapted to the special requirements set by working with such small quantities, while the weighings are carried out on a micro-balance, which has a sensitivity of 0.001 mg. The KJELDAHL method can also be carried out as a micro-method. The determination of the composition and the structure of numerous compounds of very great importance for physiology, such as vitamins, hormones and enzymes, has only become possible since these accurate micro-analytical methods have been available.

CHAPTER 3

DETERMINATION OF THE MOLECULAR WEIGHT

4. From the chemical analysis, the empirical formula of a compound is found, but not the molecular formula, since a compound of formula $C_aH_bO_c$ has the same percentage composition as $(C_aH_bO_c)_n$. In some cases a minimum value can be found by comparing the composition of the substance under investigation with the composition of a derivative obtained from the substance. The empirical formula for benzene is found to be CH. By the action of bromine on benzene, bromobenzene can be obtained with the empirical formula C_6H_5Br . This compound can be reduced again to benzene. Because not less than one bromine atom can be present in a molecule of bromobenzene, the molecule of benzene must at least be represented by C_6H_6 . The molecular formula, however, could also be $C_{12}H_{12}$, or in general $(C_6H_6)_n$. Supposing that the formula were $C_{12}H_{12}$, then that of the derivative containing bromine should be $C_{12}H_{10}Br_2$. Thus this substance would be derived from benzene by replacing two hydrogen atoms and attempts could be made to obtain a compound with the empirical formula $C_{12}H_{11}Br$. If this compound could not be prepared, the simpler formula C_6H_5Br for the bromo-derivative would become more probable, but not absolutely certain, however, since the conditions, necessary for the formation of $C_{12}H_{11}Br$, had perhaps not been discovered. It may be concluded therefore from such chemical reactions, that the molecular formula of benzene cannot be less than C_6H_6 , but not whether the formula is a multiple of this.

The molecular weight of a compound is determined by physical methods, namely, from the *vapour density* of a gaseous substance, or from the *lowering of the freezing point*, the *raising of the boiling point* or the *osmotic pressure* of a dilute solution of the substance to be examined.

Vapour density. A suitable method for the determination of the vapour density is given by VICTOR MEYER. The apparatus used (Fig. 3) consists of a glass tube *ac*, which can be closed at the top by a stopper and has a wider, cylindrical portion *ab* at the lower end with a capacity of about 200 ccs. The upper end of the tube has an exit-tube, connected by means of a thick-walled rubber tube to a gas-burette. At the same time the upper end of the tube is fitted with a side-tube, into which a glass rod is introduced

by means of a piece of rubber tubing, in such a way that it can be moved. The tube *ac* is surrounded by a wider glass (or metal) tube *ed*, in which is placed a liquid with a higher boiling point than the substance, of which the vapour density is to be determined. A thin walled glass bulb, containing a weighed amount of the substance under investigation, is now introduced at the top of the tube at *c* so that the bulb rests on the glass rod, and the liquid in *d* is brought to the boil, while the tube is still open at the top. The vapour from the boiling liquid condenses in the upper part of *ed*; after

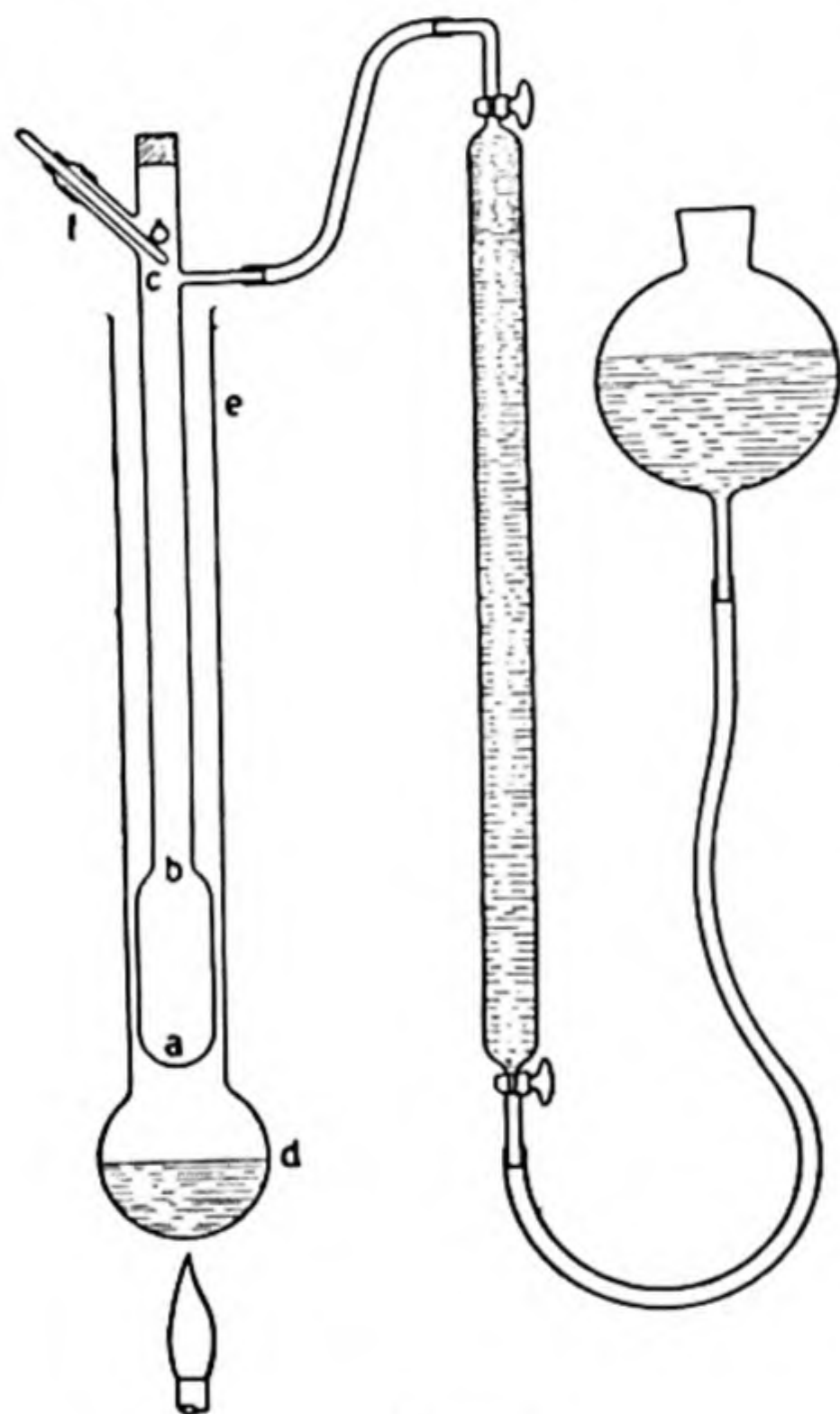


Fig. 3.

VICTOR MEYER apparatus for determination of vapour density

some time the air in *ab* has reached a constant temperature approximately equal to that of the boiling liquid. The tube *ac* is now closed with a stopper and the water in the burette is brought to the zero mark. After a check has been made that the level of the water in the burette no longer varies and therefore that the distribution of the temperature in *ac* has become stationary, the glass bulb is allowed to fall by withdrawing the glass rod at *f*. The bulb breaks and the contents quickly volatilise into the wider portion. As a result, a volume of air, which is equal to that of the amount of vapour produced, is driven over from *ac* into the measuring-tube, where it is measured. While the air in the heated part of the apparatus had the temperature prevailing there, that in the measuring tube has the temperature of the surroundings, so that this must be used in the calculations. Thus the experiment gives a volume of air, which is as large as the volume, that the weighed amount of substance would occupy in the gaseous state,

if the substance could be converted into the gaseous state at ordinary temperatures and under a pressure of one atmosphere.

A great advantage of this method over others is, that it is unnecessary to know the temperature, to which the apparatus is heated; it is essential only that the temperature shall remain constant during the short time of the experiment. This is clear from the calculation, in which temperature does not occur.

Suppose, that *g* mg. of substance have been weighed out and that the volume of air measured in the measuring-tube over water amounts to *V* ccs.,

the barometric height is H , the temperature of the air and of the water is t° and the vapour pressure of water at the temperature is b .

The volume of g mg of substance at a temperature of t° and a pressure of $H-b$ mm, is therefore V ccs., so that under these conditions $\frac{g}{V}$ mg of substance are present in unit volume (1 cc.). 1 cc. of oxygen at $H-b$ mm and t° weighs: $\frac{1.4290}{1+0.0367t} \cdot \frac{H-b}{760}$ mg, from which it follows that the vapour density D with respect to oxygen ($O = 16$) is:

$$D = 16 \times \frac{g}{V} \cdot \frac{1+0.0367t}{1.4290} \cdot \frac{760}{H-b}, \text{ and the molecular weight } M = 2D.$$

The accuracy of this method amounts to 3—5 %, which is usually sufficient for the determination of a molecular weight.

5. *Depression of the freezing point.* The freezing point of a solution, *i.e.* that temperature at which the solvent just begins to crystallise, is lower than the freezing point of the pure solvent. *The theory of dilute solutions* (VAN 'T HOFF) teaches, that the difference in freezing point between pure solvent and a dilute solution, the *lowering of the freezing point*, which is designated by the letter Δ , does not depend on the nature of the dissolved substance, but only on its molecular weight and the nature of the solvent. In this connection, substances which dissociate in solution (electrolytes) are left out of consideration. Thus if a grammolecule of one substance or another is dissolved in 100 g of a particular solvent, this solution always shows the same lowering of the freezing point, no matter what substance has been dissolved.

Therefore the freezing point of the substance, which is to serve as the solvent, is first of all determined. Then a dilute solution is prepared from this solvent and a known concentration of a compound, the molecular weight of which has been determined from its vapour density. From the lowering of the freezing point found, one calculates the lowering of the freezing point which would result from a solution of a molecule of the dissolved substance in 1000 g of solvent. This number, which from the above is a constant for a given solvent, is called the *molecular depression of the freezing point* of the solvent; this constant is represented by the letter K .

If now a solution containing a gram of a substance of unknown molecular weight M , in 1000 grams of solvent, shows a lowering of the freezing point of Δ° , the following ratio holds:

$$\Delta : K = a : M$$

from which M can therefore be calculated.

Table I gives the *molecular depressions of the freezing point* for a number of solvents. The "calculated" figures are found from the formula $K = \frac{1.98T^2}{W}$ in which K is the molecular depression of the freezing point, T is the absolute temperature of the freezing point of the solvent and W is the latent heat of fusion in gram-calories per 1000 grams of solvent (VAN 'T HOFF). Thus the latent heat of fusion of the solvent can be calculated from the depression of the freezing point brought about by a substance of known molecular weight.

The same formula holds for calculating the *molecular elevation of the boiling point*; T is then absolute temperature of the boiling point of the solvent and W the latent heat of evaporation of a 1000 grams of solvent.

TABLE I
MOLECULAR DEPRESSIONS OF FREEZING POINT

Solvent	Melting point	Molecular depression of the freezing point	
		Found	Calculated
Water	0°	1.86	1.86
Acetic acid	16.67°	3.9	3.88
Benzene	5.49°	5.13	5.3
Nitrobenzene	5.67°	6.89	6.9
Phenol	42°	7.5	7.7
Naphthalene	80.1°	6.9	6.9
Urethan	49°	5.1	
1,2-Dibromoethane	9.98°	12.5	
p-Toluidine	42°	5.2	
Camphor	180°	40	

The molecular depression of the freezing point is very high for camphor. Therefore when camphor is used as solvent the lowering of the freezing point can be measured with an ordinary thermometer divided in degrees and it is not necessary to use a thermometer, calibrated in tenths of a degree or less (JOUNIAUX). A method in which camphor is used as the solvent for determining the lowering of the freezing point with very small quantities of material (Micro-determination of the molecular weight), has been worked out by RAST.

The EYKMAN *depressimeter* (Fig. 4) is a very suitable apparatus for determining the lowering of the freezing point with sufficient accuracy for calculating the molecular weight. It consists of a short thermometer divided in 1/20 ths of a degree, with a small flask attached by means of a ground joint. The whole apparatus is placed in a glass cylinder, in which it is secured by a stopper at the upper end and underneath by cotton wool. This also serves

to retard cooling, since it is a bad conductor of heat. A weighed quantity of solvent is introduced into the flask and the freezing point determined. Subsequently a weighed amount of substance, the molecular weight of which is required, is dissolved in the solvent and the freezing point re-determined.

Example. 0.3943 g of a substance of the composition $C_7H_7ON_2$, was dissolved in 14.34 g of phenol. Hence this solution contained 27.5 g of substance per 1000 g of solvent and showed a lowering of the freezing point of 0.712° . The molecular depression of the freezing point of phenol is 7.5. Thus the molecular weight M of the dissolved substance is found from the ratio:

$$0.712 : 7.5 = 27.5 : M,$$

from which it follows that $M = 289$.

Since the formula $C_7H_7ON_2$ agrees with a molecular weight of 135 and $C_{14}H_{14}O_2N_4$ with 270, the latter value lies closest to the molecular weight found, and the double formula must therefore be ascribed to the substance under examination.

Elevation of the boiling point. The same laws hold for the elevation of the boiling points of dilute solutions as for the depression of the freezing points. The *molecular elevation of the boiling point*, i.e. the difference in boiling point between the pure solvent and the boiling point of a solution containing 1 mol of dissolved substance per 1000 g of solvent, is again a constant for a given solvent. The ratio $\Delta : K = a : M$, in which Δ represents the observed increase in boiling point of a solution containing a g of substance per 1000 g of solvent and K is the molecular elevation of the boiling point of

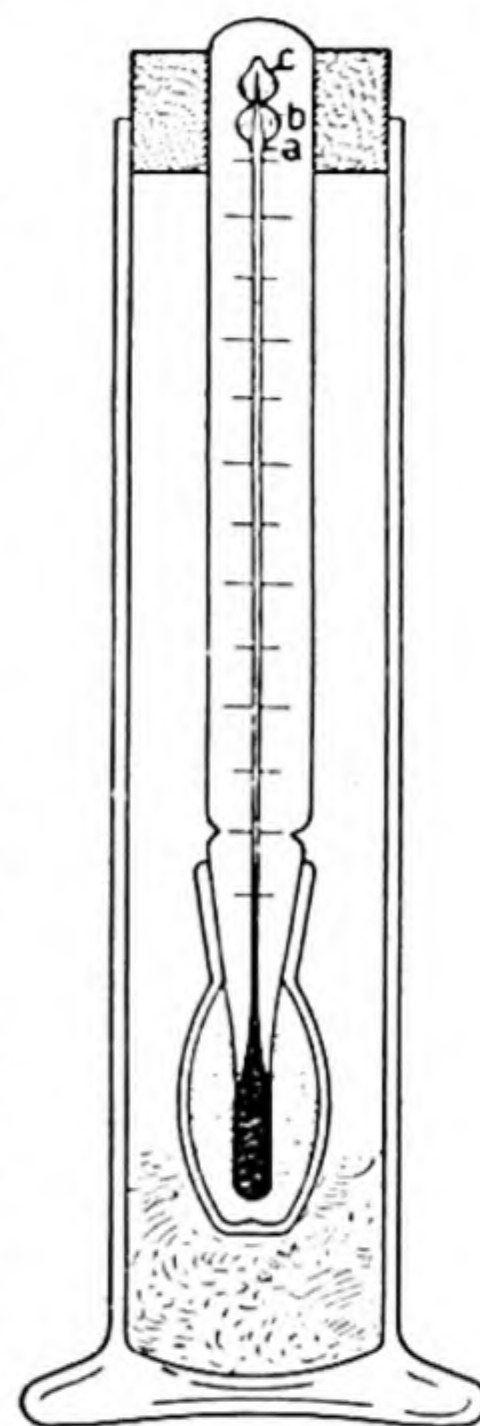


Fig. 4. EYKMAN depressimeter

TABLE 2
MOLECULAR ELEVATIONS OF BOILING POINT

Solvent	Boiling point	Molecular elevation of the boiling point	
		Found	Calculated
Water	100.0°	0.515	0.52
Diethyl ether	34.6°	2.16	2.1
Ethanol	78.3°	1.20	1.15
Acetone	56.1°	1.73	1.67
Chloroform	61.2°	3.88	3.7
Carbon disulphide	46.3°	2.29	
Benzene	80.5°	2.57	2.67
1,2-Dibromoethane	132°	6.43	
Phenol	180.5°	3.60	

the solvent, is again valid. The value of K for a number of solvents is given in Table 2. It will be seen that the molecular elevation of the boiling point is always smaller than the molecular depression of the freezing point. Therefore the ebullioscopic method is less accurate than the cryoscopic method.

EYKMAN has also described a practical apparatus for determining the rise in the boiling point, which is depicted in Fig. 5.

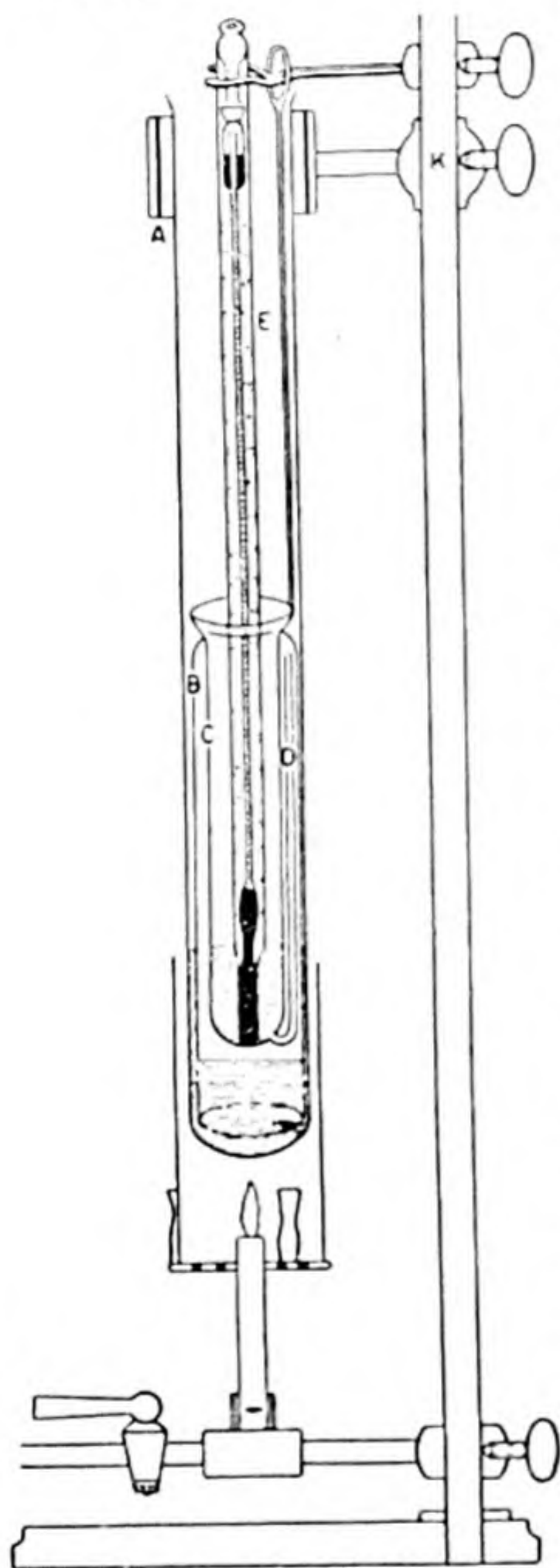


Fig. 5. EYKMAN apparatus for the determination of the elevation of the boiling point

Besides the thermometer it consists of two glass divisions; A, about 40 cm long and about 4 cm wide, acting simultaneously as a boiling jacket for the pure solvent and as an air condenser, and B, only a few mm narrower than A, to which the actual boiling vessel C with its narrow side-tube D, is sealed. This vessel can be raised or lowered by means of the platinum wire E. The thermometer scale is divided in $1/10$ ths of a degree so that it can be estimated to $1/100$ ths of a degree with a lense. It serves therefore for reading the boiling temperature and also for determining the volume of solution present in the boiling vessel. For this purpose it is calibrated beforehand with the thermometer in position, which can be done quite easily either by weighing or by direct measurement.

5–10 ml of solvent are introduced into the vessel C, so that the liquid reaches to about the beginning of the thermometer scale, while 40–50 ml of solvent are placed in the boiling jacket. The apparatus is now heated with a small flame until the vapour condenses at a constant height in the tube A (at about the height of the letter E in the figure). The thermometer is read off as the temperature becomes constant. The clamp is now moved so far upwards that the top edge of vessel C reaches a few cm out of the boiling jacket, a weighed amount of the substance to be examined is introduced into the boiling vessel, after which

it is again lowered slowly into the jacket A. The boiling point of the solution formed in the boiling vessel is higher than the boiling point of the pure solvent; the vapour of the boiling solvent, which enters the bottom of the boiling vessel through the sidetube D, therefore condenses in the solution. On account of the latent heat, which is liberated, the temperature

of the liquid rises until the boiling point of the solution is reached; the temperature then changes no further as more vapour is passed through. The temperature is again read, the vessel C is again lifted out of the vapour in the jacket and the position of the meniscus of the solution is read off as accurately as possible on the thermometer scale. The volume of the solution is calculated from the previous calibration.

Since, in this case, the volume of the solution is determined, it is convenient to calculate the constant on the volume, by dividing the value by the specific gravity of the liquid at the boiling point. The figures then become for water 0.53; acetone 2.3; ethanol 1.58; benzene 3.08.

CHAPTER 4

METHODS FOR THE SEPARATION AND IDENTIFICATION OF ORGANIC COMPOUNDS; DETERMINATION OF SOME PHYSICAL CONSTANTS

(i) METHODS OF SEPARATION

6. *Distillation.* The separation of a liquid mixture by distillation depends on the difference in volatility of the constituents. The simplest set up for a distillation is given in Fig. 6. The liquid is brought to the boil in the distillation flask, which also contains a few pieces of porous pot ("boiling

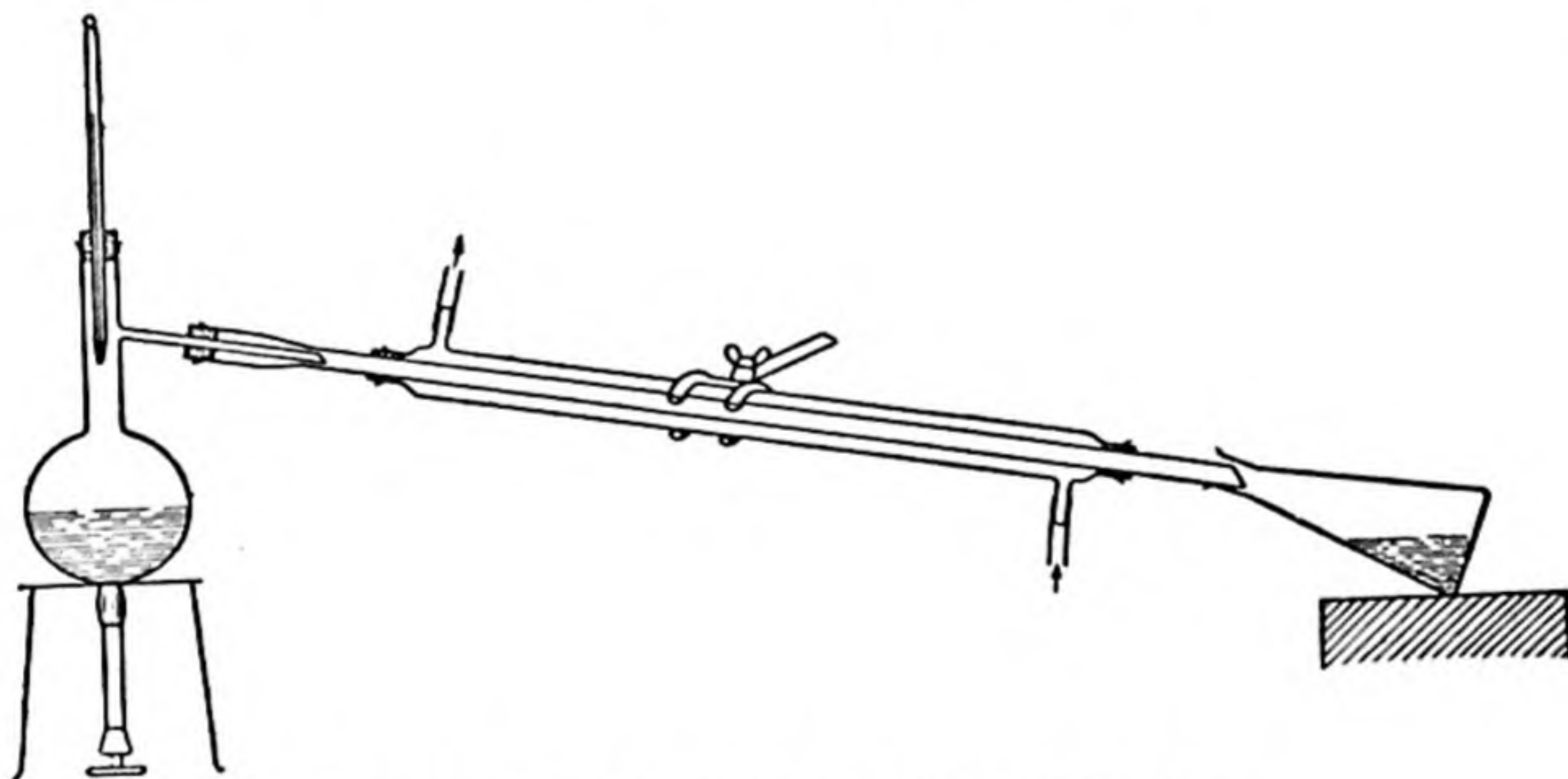


Fig. 6. Simplest set up for distillation

stones") to facilitate smooth boiling. The vapour which escapes from the boiling liquid, contains more of the most volatile constituent than the liquid. This vapour passes through the side-tube into the condenser, where it is condensed; the distillate which passes over at the beginning of the distillation therefore contains more of the most volatile component than the original liquid mixture. As the distillation is continued the temperature of the boiling liquid rises, while the composition of this liquid and that of the vapour co-existing with it gradually alters. Thus the distillate can be collected in different fractions. By systematically repeating this process,

i.e. by *fractional distillation*, in which the extreme fractions, *i.e.* the most volatile and the least volatile, are separated and the middle fractions are collected together and again distilled between narrow temperature limits, in many cases an almost complete separation can be achieved.

For obtaining a closer view of what occurs in the distillation of liquid mixtures, it is useful to consider the boiling points curve of a binary mixture; such a curve gives the relationship between the composition of the boiling liquid and the co-existing vapour. The general shape of the different types of boiling points curves can be derived from the theory of binary mixtures (KONOWALOW, VAN DER WAALS, BAKHUIS ROOZEBOOM). Similar curves have also been determined experimentally for a number of mixtures of liquids. Fig. 7 gives the simplest form of a boiling points curve for a mixture of two liquids A and B which are miscible in all proportions.

The horizontal axis represents the composition of the mixture from 100 % A to 100 % B. The temperature is given along the vertical axis; the curve is valid for a particular pressure, another curve, usually of the same type, holds for each other pressure. If the pressure is one atmosphere then *a* represents the boiling point of the most volatile component A, and *b* the boiling point of the least volatile component B. The curve *aecb* gives the temperatures, at which mixtures from 100 % A to 100 % B begin to boil. In general, this curve is not a straight line, which indicates, that the boiling point of a mixture of liquids does not as a rule vary linearly with the composition, although in many cases the deviation is not great. The composition of the vapour, corresponding to the boiling liquid, is given by the curve *afdb*. At *a* and *b*, *i.e.* for each of the components separately, the composition of the vapour is identical with that of the liquid; for all other mixtures the vapour is richer in A than the coexisting liquid.

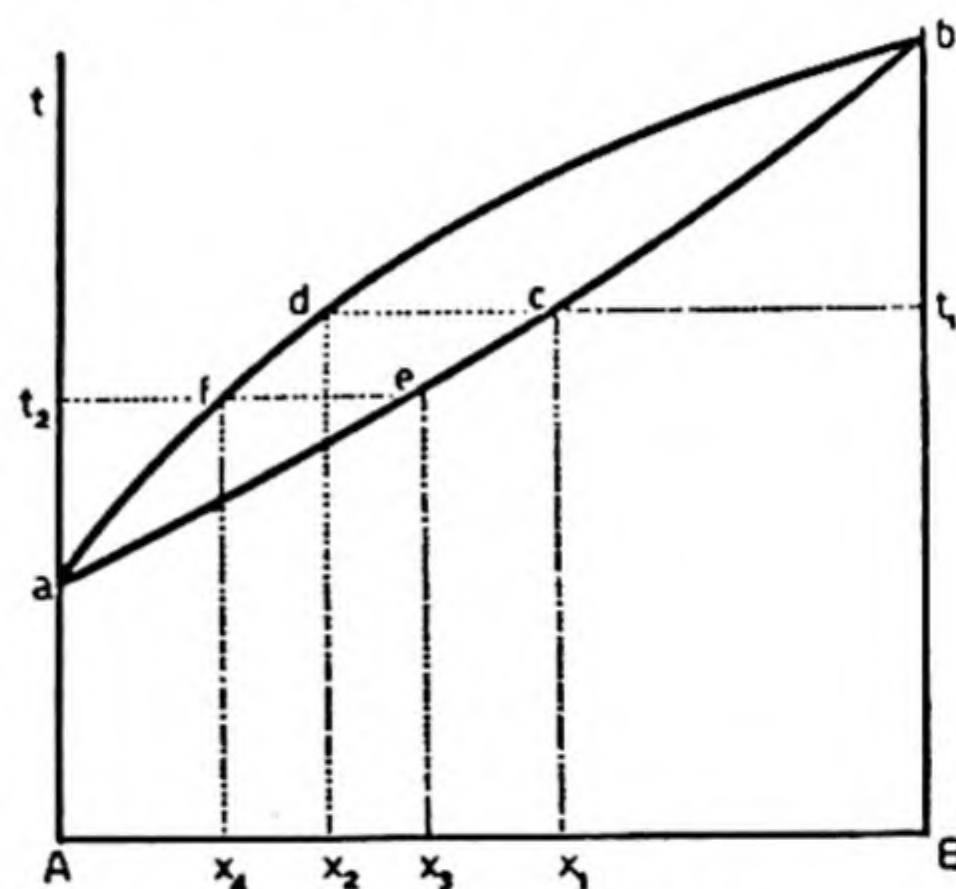


Fig. 7. Boiling points curve for two liquids miscible in all proportions

If a liquid mixture of composition x_1 is heated, it begins to boil at a temperature t_1 , which corresponds with the point *c*; the composition of the vapour *d*, which is evolved at the first moment of boiling, is given by x_2 . Because the coexisting vapour and liquid are at the same temperature, *c* and *d* lie in a horizontal line. If the vapour *d* is lead off into the condenser, the liquid becomes poorer in A and the temperature of the boiling point rises; the composition and the temperature of the boiling liquid alters according to the curve *cb* and that of the vapour according to the curve *db*.

In actual practice in carrying out a distillation, however, the vapour *d* is cooled on its way from the boiling liquid to the condenser, for example, to a temperature t_2 ; the consequence of this is, that a part of this vapour is condensed to a liquid *e* of composition x_3 , which returns to the flask, while the vapour *f* of composition x_4 reaches the condenser and is recovered as the distillate. Hence by partially condensing the vapour from a boiling liquid the useful effect of the distillation is increased. This is accomplished by placing a fractionating apparatus between the boiling flask and the condenser (see Fig. 8).

The desired partial condensation of the vapour is obtained as a result of the condensing surface of this type of apparatus. The vapour rising from the flask has a higher temperature than the liquid flowing down the fractionating column; the vapour is cooled in its way upwards, the falling liquid is heated. In order to bring about this exchange in temperature as completely as possible, by which the descending liquid becomes poorer and the ascending vapour becomes richer in the component A, intimate contact between liquid and vapour is necessary. This requirement is fulfilled by the construction of the fractionation apparatus (by filling with glass rings or beads, appropriate constrictions, etc.).

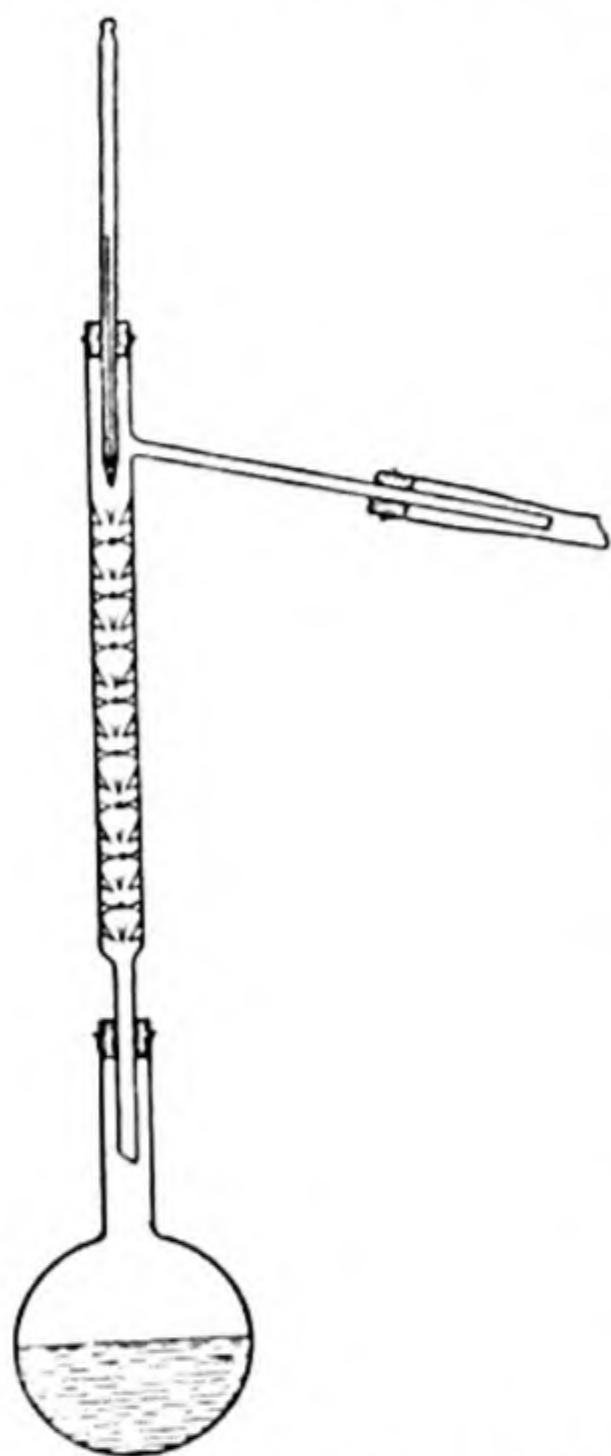


Fig. 8. Boiling flask with fractionating apparatus

A number of mixtures are known also, in which the boiling points curve shows a maximum or a minimum: Figs. 9 and 10.

At the minimum (or the maximum) the composition of the boiling liquid x_1 is the same as that of the coexisting vapour. In Fig. 9 the boiling point curve is given by $adcgb$ and the composition of the coexisting vapour by $aecfb$. The vapour f , corresponding to a liquid g , contains more of component A, the vapour e , however, contains less of A than the corresponding liquid d .

If one has a mixture, the composition of which lies between x_1 and B, it will not then be possible to separate the component A in a pure state by fractional distillation. Actually the liquid with the lowest boiling point will be separated off; this liquid will consist now not of component A, but of a mixture of x_1 % of B and $100 - x_1$ % of A. Once the composition of this mixture has been reached it is not altered by continued distillation, since for this particular mixture the composition of the vapour is identical with that of the boiling liquid. Thus this mixture behaves as far as the boiling

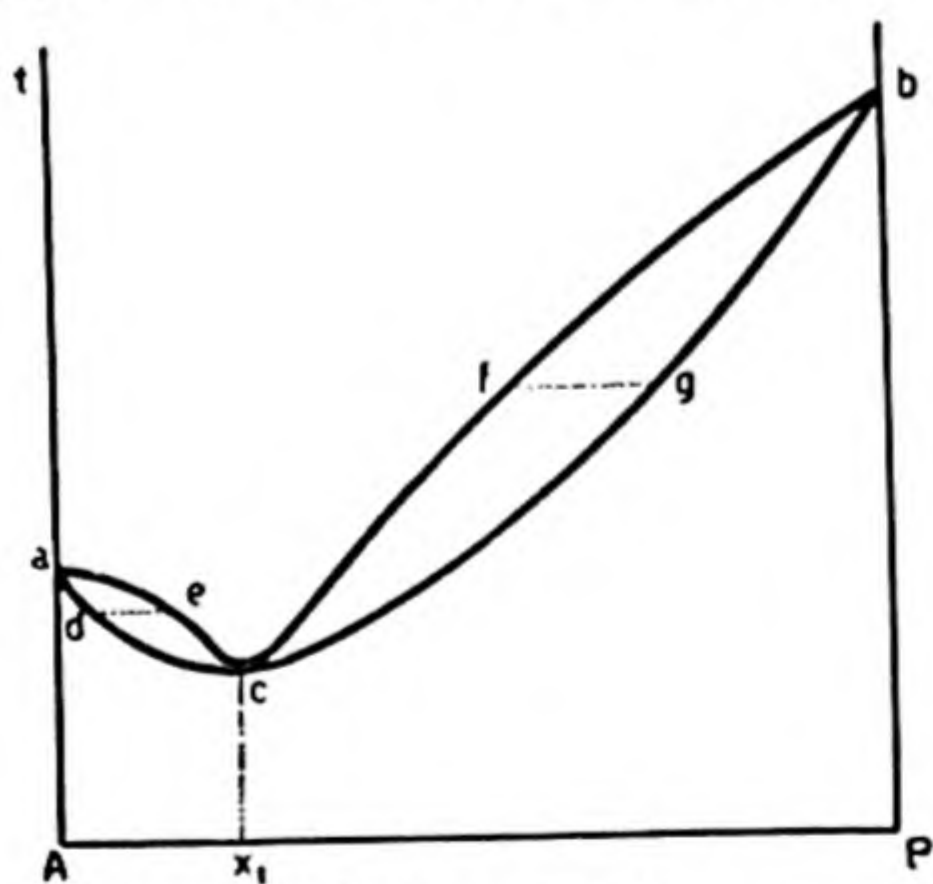


Fig. 9. Boiling points curve showing minimum

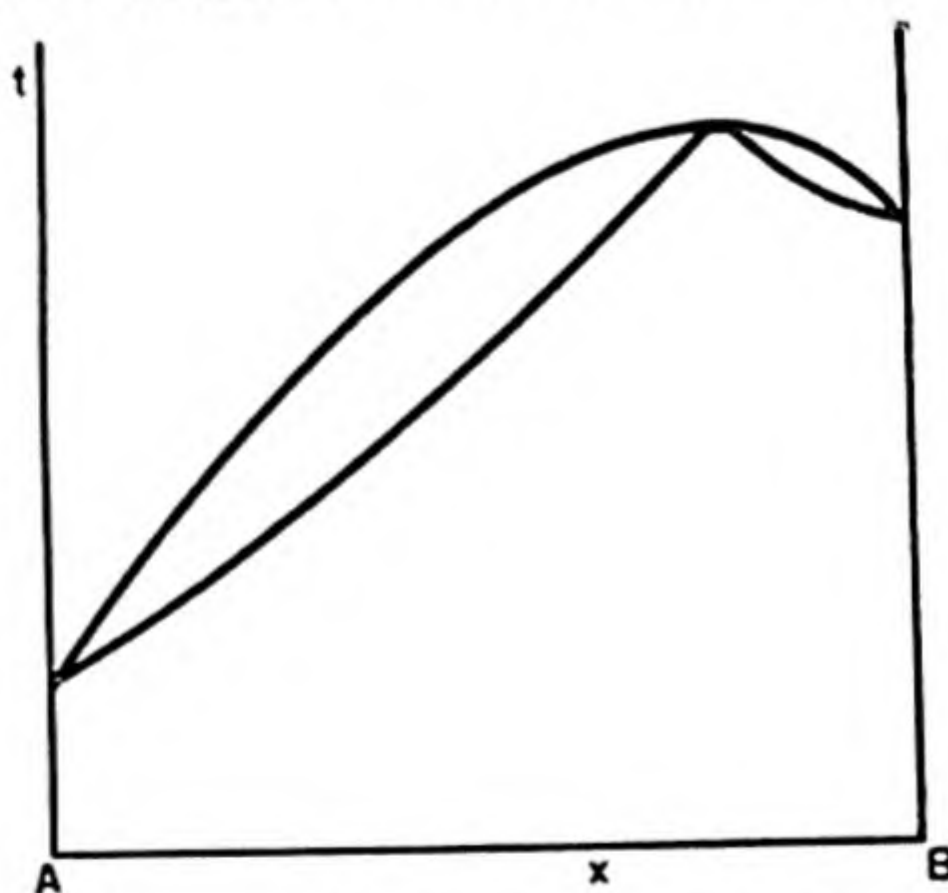


Fig. 10. Boiling points curve showing maximum

point is concerned, like a pure substance. If one starts from a mixture intermediate in composition between A and x_1 , the constant boiling mixture of composition x_1 can be separated by fractional distillation, while pure A eventually remains behind in

the distillation flask. Mixtures with a minimum or maximum boiling point are called *azeotropic mixtures*. Mixtures with minimum boiling points are found, for example, in the binary systems: ethanol—water, propanol-1—water, propanol-2—water and in a great number of other binary systems of organic liquids: *e.g.* in mixtures of alcohols with hydrocarbons, alcohols with esters, alcohols with halogeno-compounds, ketones with hydrocarbons, esters with hydrocarbons and even in mixtures of very closely related compounds such as alkanes with cyclanes. Hence in separating mixtures by distillation the possibility of azeotropy must always be taken into account; therefore a few examples are given in Table 3.

TABLE 3
AZEOTROPY

Component A	Component B	B.p. A °C	B.p. B °C	B.p. azeotropic mixture °C	% A
Ethanol	Water	78.3	100	78.15	95.57
Ethanol	Benzene	78.3	80.5	68.2	32.4
Methanol	Ethyl acetate	64.7	77.1	62.2	44
Ethanol	1,2-Dichloroethane	78.3	83.7	70.5	37
<i>n</i> -Hexane	Butanone	68.9	79.0	64.2	63
<i>n</i> -Hexane	Ethyl acetate	68.9	77.1	65.0	58
Benzene	Cyclohexane	80.5	80.8	77.65	52.5

For an example of azeotropy in a ternary mixture see 31.

Examples of liquid-pairs with a maximum boiling point are water—nitric acid, water—hydro-halogenic acid, water—formic acid and chloroform—acetone.

7. *Distillation under reduced pressure.* Many organic compounds decompose when they are heated under ordinary pressure at their boiling point. In order to purify such substances by distillation, the process is carried out at reduced pressure. At 15 mm pressure (water pump) the boiling point of many organic substances lies about 100 degrees lower than at 760 mm; by using a higher vacuum (1 to 0.01 mm) the boiling temperature can be reduced considerably further.

Distillation with steam. Substances, which have a sufficiently high vapour pressure at 100°, but possess boiling points much higher, can be volatilised by steam at 100°; the vapour of the organic compound is condensed along with the steam. In many cases, the distillation of two liquids, *e.g.* water and the substance passing over with the steam, which are not miscible in all proportions, is encountered. If two liquids, which are completely insoluble in one another are heated together to the boil, the vapour pressure of the one liquid is not altered by the presence of the other. When the two liquids boil together the total vapour pressure is equal to the atmospheric pressure; hence the partial vapour pressure of each of the two liquids is smaller than

the barometric pressure, from which it follows, that boiling occurs at a temperature, which is lower than the boiling point of the lower-boiling of the two liquids; so long as some of each of the two immiscible liquids is present in the distillation flask, the temperature and the composition of the vapour remains the same.

When chlorobenzene (b.p. 132°), is heated with water, boiling commences at 90.2° ; both substances distil over at this temperature until only one of them remains behind in the distillation flask, depending on the relative quantities, which were originally present. When this point is reached, the temperature quickly rises to the boiling point of the substance remaining behind.

Nitrobenzene boils at 210.6° ; if nitrobenzene is heated with water, the mixture distils over at 99° at an external pressure of 760 mm; at this temperature the water vapour has a pressure of 733 mm, hence the partial pressure of nitrobenzene is 27 mm. The quantities by weight of water and nitrobenzene, which are present in the vapour phase, are in the proportion of the products of the partial pressures and the molecular weights, thus as 733×18 (water): 27×123 (nitrobenzene) or approximately as 4 : 1. Notwithstanding the small vapour pressure of nitrobenzene at the temperature of distillation, this substance distils over quite rapidly, *i.e.* with relatively little water, because water has a much smaller molecular weight than nitrobenzene. Even if an organic substance has a vapour pressure of only 10 mm at the temperature of steam distillation, the process can still be carried out fairly rapidly and satisfactorily.

Thus the same end is reached by steam distillation as by distillation under reduced pressure, namely, that the substance is distilled over at a temperature lower than the boiling point of the substance at ordinary pressure. This method of distillation can also be carried out as a fractional distillation.

8. Extraction. *The separation of liquids, which do not mix*, is brought about by means of a separating funnel (Fig. 11), which also serves for the *extraction* of aqueous solutions. The aqueous solution is introduced along with a volatile liquid, which does not mix with water, such as ether, petroleum ether, chloroform, carbon disulphide, etc. in a separating funnel and shaken vigorously. The substance dissolved in water then passes partially into the organic liquid *e.g.* ether. The two liquid layers are then separated. Since some water also dissolves in the ether, the ethereal liquid is freed from the dissolved water (dried) by means of calcium chloride or another dehydrating agent; the required substance remains behind after distilling off the ether. This extraction will quickly lead to the desired result if the substance to be isolated is much more soluble in the organic solvent used than in water; practically all the substance can be extracted from the water by a few

successive extractions. On the other hand if the substance is more soluble in water, then even after several extractions considerable quantities still remain behind in the aqueous liquid.

If two immiscible liquids are in contact with a substance, which is soluble in both, this substance will divide itself between the two solvents, in such a way that the ratio between the concentrations of the substance in the respective solvents will be a constant value (BERTHELOT's partition rule).

If a solution of x_0 grams of substance dissolved in a grams of solvent (water) is shaken with b grams of a second solvent (ether), then a quantity x_1 of dissolved substance will remain behind in the first solvent (water), while a quantity $x_0 - x_1$ will pass over into the second solvent. Now according to the partition rule, the following equation holds: $\frac{x_1}{a} = k \cdot \frac{x_0 - x_1}{b}$, in which the *partition coefficient* k

represents the constant ratio between the concentrations in the two solvents. From this follows: $x_1 = x_0 \frac{ka}{b + ka}$, x_1 is thus the quantity

remaining behind in a grams of solvent after one extraction; after two successive extractions of these a grams with b grams of the second solvent, there remains in the first solvent: $x_2 = x_0 \left(\frac{ka}{b + ka} \right)^2$ and after n extractions $x_n = \left(\frac{ka}{b + ka} \right)^n$.

If one extracts n times, each time with $\frac{b}{n}$ grams of the second solvent, then after the n th time there remains in the original solvent:

$$x_n = x_0 \left(\frac{ka}{\frac{b}{n} + ka} \right)^n = x_0 \left(\frac{1}{\frac{b}{a \cdot n \cdot k} + 1} \right)^n$$

The useful effect, which can be obtained by extraction, is greatly dependent on the value of the partition coefficient.

Calculation shows, that it is more efficient to extract the aqueous solution repeatedly with small portions of the second solvent, than to use the whole quantity of the second solvent at one time. This is clearly apparent from Table 4 (SPIERS), in which the value

is given of $\left(\frac{1}{\frac{b}{a \cdot n \cdot k} + 1} \right)^n$ for different values of k , each time with different values of a , b and n .

A few examples will clarify this table. The partition coefficient of nitrobenzoic acid between water and ether is 0.1, i.e. if the concentration of a solution of nitrobenzoic acid in water is represented as 1, the concentration of the solution of nitrobenzoic acid in ether, which is in equilibrium with the first solution, equals 10.

If 100 grams of a solution of nitrobenzoic acid in water is extracted 4 times, each time with $\frac{25}{4}$ grams of ether ($a = 100$, $b = 25$, $n = 4$) 0.143 of the original quantity of nitrobenzoic acid will remain behind in the aqueous solution. If 100 grams of the aqueous solution are extracted 4 times, each time with $\frac{100}{4}$ grams of ether, then

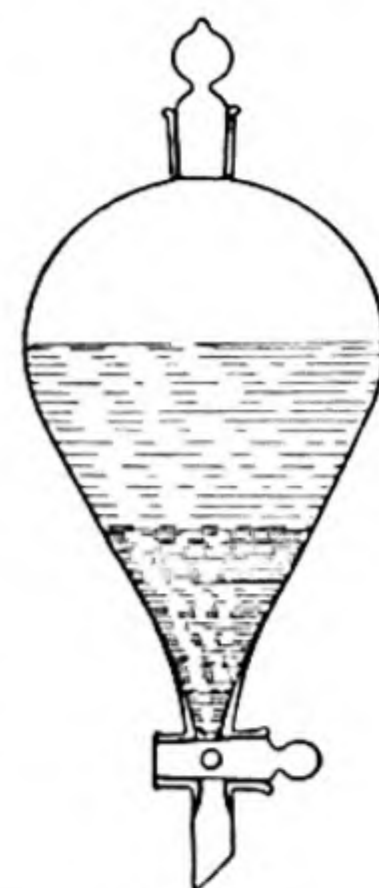


Fig. 11.
Separating
funnel

0.0067 of the original quantity of nitrobenzoic acid will still be present, but on the other hand, only 0.0015 if the solution is extracted 8 times with $\frac{100}{8}$ grams of ether.

TABLE 4
EFFICIENCY OF EXTRACTION

k	b = 1/4a			b = a			b = 4a		
	n = 4	n = 8	n = ∞	n = 4	n = 8	n = ∞	n = 4	n = 8	n = ∞
0.1	0.143	0.114	0.082	0.0067	0.0015	4.5×10^{-5}	7×10^{-5}	6×10^{-7}	4×10^{-18}
0.5	0.624	0.616	0.607	0.198	0.168	0.135	0.012	0.0039	0.00034
1	0.785	0.782	0.779	0.410	0.390	0.368	0.062	0.039	0.018
2	0.884	0.883	0.882	0.624	0.616	0.606	0.198	0.168	0.135
10	0.975	0.975	0.975	0.906	0.905	0.905	0.683	0.677	0.670
							b = 20a		
							n = 4	n = 8	n = ∞
10							0.198	0.168	0.135

The partition coefficient of lactic acid between water and ether is 11. If 80 % of the lactic acid present in an aqueous solution is to be extracted with ether it should require the use of 20 times as much ether as aqueous solution to be extracted (see the values in the Table for $k = 10$). Furthermore, it appears, that if k has a high value, it makes very little difference whether the extraction is carried out with the whole quantity of the second solvent in one operation, or in a large number with small quantities at a time. In such cases, a continuous process is employed, in which the ether, for example, is allowed to bubble through the aqueous solution to be extracted. The ethereal solution is distilled, when the extracted material remains behind and the ether, which distils off, is again led through the liquid being extracted (*perforation*).

In table 5 are given for a few substances, the experimentally determined values for the partition coefficients between water and a second solvent.

9. *Separation of crystalline substances by fractional crystallisation.* This method of separation depends on differences in solubility. The mixture is dissolved in the least possible quantity of a solvent at its boiling point and allowed to cool; the component having the lowest solubility at the temperature to which the mixture is cooled, crystallises out first. From the mother liquors, which are separated by filtering off the crystals, a crystalline fraction separates on further cooling or after concentration by evaporation, which consists mainly of the more soluble component. By repeating this treatment a few times, the components of the mixture are finally separated from one another. For the successful application of this method it is necessary that the solubility of the substances under investigation, increases sufficiently as the temperature is increased and, that the solubilities of the different components in the chosen solvent diverge sufficiently.

TABLE 5
PARTITION COEFFICIENTS

	Partition coefficient between water and				
	ether	petroleum ether	benzene	chloroform	methyl ethyl ketone
Acetic acid	2.1 (25°)	200	28 (25°)	15 (25°)	0.9 (25°)
<i>n</i> -Butyric acid	0.16 (25°)	9	0.18	0.8 (25°)	0.03 (25°)
<i>n</i> -Valeric acid	0.04 (22°)	10.2			0.1 (25°)
<i>n</i> -Caproic acid	0.01 (23°)	0.2	0.08	0.03 (25°)	
Oxalic acid	9 (15°)				
Succinic acid	6 (15°)				
Lactic acid	11 (27°)				
Tartaric acid	250 (27°)				
Benzoic acid	0.014	1.0 (20°)		0.08	
Salicylic acid	0.004 (15°)		0.4 (25°)	0.3 (25°)	
Phenol			0.5 (25°)	0.3 (25°)	
Picric acid	0.5	> 1	0.5 (20°)	0.3 (25°)	
<i>m</i> -Nitrobenzoic acid	0.1		0.4 (20°)	0.06	
Methylamine	> 1		25 (25°)	12	
Trimethylamine	2.4 (20°)		2.0		

Separation by fractional crystallisation is impossible, if the components of the mixture form mixed crystals, since in this case the crystals which separate are composed of both components.

(ii) CHARACTERISTICS OF PURITY AND THE IDENTIFICATION OF ORGANIC COMPOUNDS BY MEANS OF PHYSICAL CONSTANTS

10. In principle the determination of any physical constant can serve as a characteristic for the purity of a chemical compound. The physical constants which come into consideration for this purpose are, for example, the melting point, the boiling point, with liquids the specific gravity and the refractive index, the optical rotatory power (of optically active substances). Determination of the crystalline form may also be of considerable help in identifying a substance.

The *determination of the melting point* has great practical significance. A mixture of two (or more) substances does not melt at one temperature, but the melting takes place over a temperature range; the temperature at which everything is melted, usually lies lower than the melting temperature of either of the substances separately. An exception to this rule can occur only with substances which form a continuous series of mixed crystals. Hence, if a substance is recrystallised—preferably from different solvents—

until the melting point no longer changes on repeating the process, it may be concluded, with a high degree of probability, that the preparation consists of one chemical compound. Further, it follows, that if a mixture of two substances A and B shows the same melting point as each of the substances A and B separately, these substances are identical.

On this fact depends the *mixed melting point test*, which is very frequently used to decide whether two crystalline preparations, which are expected to consist of the same chemical compound, are actually identical.

In observing melting points and drawing conclusions from them, account has to be taken also of the possibility of *polymorphism*, by which is understood, that the same chemical compound can occur in different crystalline modifications, showing different melting points. A number of examples of such dimorphous substances are already known among organic compounds.

In the practice of organic-chemical research it is in many cases sufficient to determine the melting point with an accuracy of 0.5 to 1.0°C . 10–20 Milligrams of the substance are introduced into a narrow, thin-walled, glass tube, sealed at one end, which is then fixed to a thermometer by means of a small rubber ring, in such a way that the substance is situated at the same height as the mercury reservoir. The thermometer is then placed in a high-boiling liquid (paraffin oil); the melting point apparatus is set up in such a way that the temperature of the liquid surrounding the thermometer slowly and regularly rises. The temperature is read off at the moment when the crystals melt. Sometimes, it is preferable to determine the setting point instead of the melting point. The test is then carried out with a few grams of substance; the thermometer is placed in the molten substance.

The determination of the boiling point is usually carried out in a fractionating flask, from which the liquid is at the same time distilled. It also applies here, that a mixture does not boil at one definite temperature, but within a range of temperatures. Now, however, the temperature at which the mixture begins to boil, may be either higher or lower than the boiling point of the pure substance, according to whether the impurity boils higher or lower; this is clearly apparent from a consideration of the boiling-points curve (see p. 24). A boiling point is not so easily determined with an accuracy of 0.1° as a melting point or a setting point, partly on account of the effect of atmospheric pressure. With liquids the determination of the specific gravity and of the refractive index can be a very good criterion of the purity.

11. Specific gravity. The specific gravity of organic liquids alters considerably with the temperature, since the coefficient of expansion of organic liquids is nearly always much greater than that of water. The specific gravity is usually measured with a pycnometer, (cf. Fig. 12).

The specific gravity (or density) of an organic compound, depends on the number and the kind of atoms in the molecule, and also on the arrangement of these atoms, *i.e.* on the chemical structure. When the molecular weight of a compound is divided by the density then the value obtained is the volume occupied by a mole of the substance at the temperature at which the density is carried out. This quantity is called the *molecular volume*. The molecular volumes calculated in this way, however, are proportional to the actual volumes of the molecules only to a first approximation in accordance with the molecular theory of liquids.

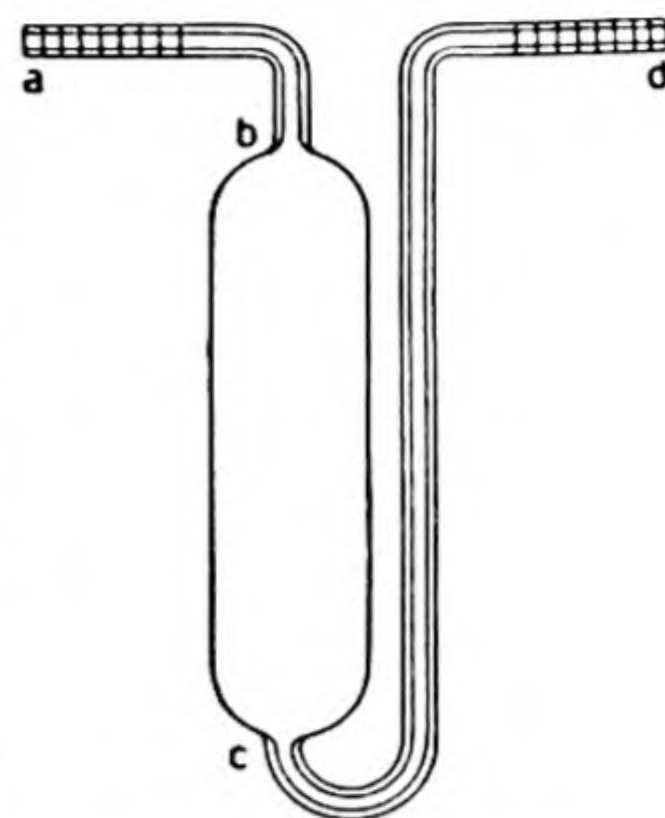


Fig. 12.
EYKMAN pycnometer

12. Refractive index and molecular refraction. The *refractive index* n is dependent on the wave-length of the light; in accurate measurements, therefore, the value of n is determined for a definite wave-length, *e.g.* for the D-line of the sodium spectrum, or for the $H\alpha$ -, $H\beta$ - and $H\gamma$ -lines of the hydrogen spectrum or for certain lines in the helium spectrum (PULFRICH and EYKMAN refractometers). The refractive index is also dependent on the temperature, so that this must be accurately determined during the measurement. If the greatest accuracy is not required the refractive index for the D-line can be determined with the ABBE refractometer. The determination of the refractive index is frequently used as a criterion for the purity of a liquid compound, because the value found is clearly influenced by small quantities of other substances which may occur in the preparation. Also mixtures of two substances can be analysed by means of the refractive index, if the values for the pure components are known.

On theoretical grounds H. A. LORENTZ has demonstrated that the expression $\frac{n^2 - 1}{n^2 + 2} \cdot \frac{1}{d}$, where n represents the refractive index and d the density, must be independent of the temperature. When this expression is multiplied by the molecular weight M of the compound under investigation, the product $\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d}$ is called the *molecular refraction*.

From a great many investigations (BRÜHL, EYKMAN, AUWERS, *et al.*) it appears, that not only does the molecular refraction depend on the number and the kind of the atoms in the molecule, but is dependent also on the arrangement of these atoms, *i.e.* on the structure of the molecule. The difference in the molecular refractions for different wave-lengths is

called the *molecular dispersion*; this quantity also is connected with chemical structure.

Accurate observations have taught, that the values of the molecular refraction, calculated by the LORENTZ formula, are not quite independent of the temperature, which must be ascribed to the fact that the suppositions on which the formula is based, are not strictly valid.

From a large number of observations EYKMAN has derived an empirical equation, which satisfies the requirement of independence of the temperature more satisfactorily than the formula of LORENTZ, namely: $\frac{n^2 - 1}{n + 0.4} \cdot \frac{M}{d}$.

The value calculated by this equation is not therefore identical with the molecular refraction but has the significance of an empirical constant.

13. Rotation of the plane of polarisation. When polarised light is passed through a layer of turpentine or of a sugar solution, it is observed, that the direction of vibration of the emergent beam is altered with regard to that of the incident beam; the liquid has the property of bringing about a *rotation of the plane of polarisation*. A large number of organic compounds is known, which either in the *liquid or in the dissolved state*, cause a rotation of the plane of polarisation; this phenomenon was discovered by BIOT (1815). The substances are said to be *optically active*. Examples of optically active compounds are, for example, cane sugar, glucose, menthol, quinine, camphor.

It will appear later, that this property is of fundamental importance for information regarding the structure of organic compounds (37). The optical activity is also used for analytical purposes.

The rotation of the plane of polarisation is measured in a *polarimeter*, in which a beam of polarised light passes through a tube of accurately known length (usually 100 or 200 mm), containing the solution of the optically active substance or the pure compound if a liquid. The angle, through which the plane of polarisation is rotated, is dependent on the nature of the optically active substance, on the wave-length of the light, and is directly proportional to the thickness of the liquid layer traversed by the polarised light. At the same time this angle is usually slightly dependent on the temperature, but this need only to be taken into account in very accurate measurements. The rotation of the plane of polarisation is therefore determined for light of a definite wave-length, usually for sodium light (D-line). The rotation produced by any particular substance in a tube of given length, *i.e.* the angle, read off directly on the instrument, is designated by α . It has been agreed, that by the term *specific rotation* shall be understood the angle α , divided by the length l of the tube containing the liquid (measured in decimeters) and divided by the specific gravity of the liquid d . This

specific rotation is designated by $[\alpha]$. The wave-length of light for which α is determined is given by a letter (thus usually D). One has therefore

$$[\alpha_D] = \frac{\alpha_D}{ld}.$$

With solutions of an optically active substance the rotation is dependent also on the nature of the solvent and on the concentration of the solution; the amount of the rotation is not always proportional to the concentration of the optically active substance (abnormal rotation). If a solution contains p grams of optically active substance in 100 grams of solution and d is the specific gravity of the solution, the specific rotation of the dissolved substance is represented by $[\alpha_D] = \frac{\alpha_D \cdot 100}{p \cdot l \cdot d}$.

Absorption spectra. When a beam of white light passes through a liquid, which absorbs light of definite wave-lengths, the spectrum of the emergent light shows dark bands, called absorption bands, which correspond with the wave-lengths of the absorbed light. The liquid is then coloured.

With many substances, which are colourless and therefore show no selective absorption in the visible part of the spectrum, selective absorption occurs in the ultra-violet part of the spectrum. The wave-length of the light is expressed in Ångström units, which are denoted by the sign Å; the micron is also used as a unit. The Ångström unit = 10^{-8} cm., the micron (μ) = 10^{-4} cm. The wave-length of visible light lies between about 8000 and 4000 Å, that of ultra-violet light between 4000 and 1000 Å.

The determination of absorption spectra in the visible region and in the ultra-violet is frequently of importance for the identification of compounds, for testing a proposed structural formula or for investigations on tautomerism. For these determinations the substance under investigation is dissolved in a solvent, which itself shows no specific absorption in the region to be examined.

Absorption spectrum in the ultra-violet. In this case *n*-hexane or *n*-heptane, which show practically no absorption in the ultra-violet, or ethanol, which shows only a slight absorption, are used as solvents. It is essential to carry out the measurements with very dilute solutions to ensure that the mutual interaction between the molecules of the dissolved substance is as small as possible, since this interaction influences the absorption spectrum. Many qualitative data became known from the original investigations on the ultra-violet absorption spectra of liquids carried out by HARTLEY round about 1880. Later, various investigators, like BAILEY, VICTOR HENRI, SCHEIBE, improved the technique and made it suitable for quantitative measurements. The absorption is proportional to the number of absorbing molecules, which the beam of light encounters in its path, hence with the concentration c of the solution (in moles per litre), and with the thickness d of the layer of liquid (BEER'S Law).

The *extinction coefficient* e is defined as $e = \frac{1}{cd} \log \frac{I_0}{I}$, in which I_0 and I represent the intensity of the incident and the emergent light, respectively.

As a light source in these measurements may be used either an electric arc between iron electrodes, which gives a spectrum rich in lines in the ultra-violet or a hydrogen discharge tube, which gives a continuous spectrum in the ultra-violet. With a spectrograph fitted with quartz lenses and prism, it is possible to obtain spectra in the region

of 4000 — 2000 Å. The beam of light emerging from the liquid is resolved by the prism. The intensity of the ray of light of definite wave-length leaving the prism, can be determined by a photographic method or by photoelectric measurements. The intensity I of a ray of light, which has passed through the solution, and the intensity I_0 of a similar ray of light of the same wave-length, which has traversed the pure solvent, are determined; the thickness of the layer of the solvent and that of the solution must be identical. The values of e , which are set out as ordinates against the corresponding values of the wave-length λ , as abscissae, are then calculated from the data obtained. In this way an *extinction curve* is obtained, which may show one or more maxima.

An absorption band is characterised by the values of e and λ of a maximum in the extinction curve. If, on the absorption of light, one electron were to be raised to a higher energy level only, then only one particular wave-length in the visible or ultra-violet spectrum should be absorbed and an absorption line should be observed. A more or less broad absorption band is observed, however, because part of the incident light-energy is converted into vibrational and rotational energy.

Since the ultra-violet absorption spectrum represents the result of the absorption of light-energy on account of electron displacements, vibrations and rotations together, this spectrum is characteristic of the molecule as a whole. By comparing the extinction curves of a number of different compounds, all of which contain a characteristic group, in some cases a definite absorption band can be ascribed to a particular group of atoms (cf. 59, 250, 251).

Selective absorption in the ultra-violet is not observed in completely saturated compounds such as the alkanes, but it does occur with unsaturated hydrocarbons, aldehydes and ketones, carboxylic acids, nitriles, etc.

All organic compounds show selective absorption in the *infra-red* part of the spectrum extending from 0.8 to 20 microns. From *infra-red absorption spectra* it is possible to derive the frequencies of *vibration* (oscillation of two atomic nuclei in the direction of their bond of union) and of *rotation* (in a bi-atomic molecule the rotation about an axis at right angles to the bond of union between the atoms). Rotational and vibrational frequencies provide data on the positions of the atomic nuclei in a molecule and their mutual distances.

Raman-effect. When a beam of monochromatic light passes through a liquid a small proportion of the light is scattered in a direction perpendicular to the direction of the incident beam. In the spectrum of this scattered light one observes not only the lines of the incident light, but also weak lines on either side of the lines expected (RAMAN 1928). The difference in the wave number between the incident and the scattered light, the *Raman frequency*, $\Delta\nu$, is expressed in reciprocal wave-lengths ($1/\lambda$), i.e. the number of waves per cm. From the magnitude of $\Delta\nu$ it can be deduced that these frequencies correspond to vibrational transitions. (cf. 37, p. 70).

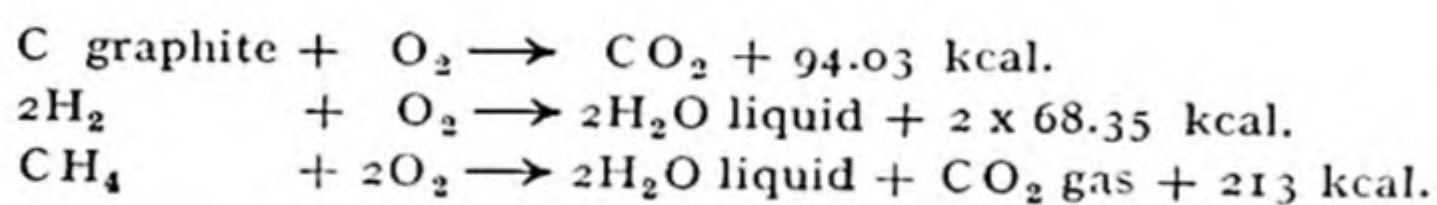
14. Heat of combustion. A knowledge of the *heat of combustion* of organic substances is of importance both from a theoretical point of view and for practical purposes (heating value of fuels).

By *molecular heat of combustion* is meant the quantity of heat, measured in kilogram-calories, which is set free when a gram-molecule of the substance is burnt to carbon dioxide and water (with nitrogenous compounds free nitrogen is also produced). The heat of combustion is known for a large

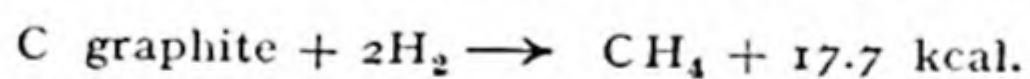
number of organic compounds from the older investigations of J. THOMSEN, BERTHELOT, STOHMANN and from the newer, more accurate, measurements of ROTH, RICHARDS, VERKADE, COOPS and ROSSINI. The determination is carried out by a method devised by BERTHELOT and VIEILLE, in which the substance under investigation is burnt in compressed oxygen in a steel cylinder (BERTHELOT bomb). The bomb is placed in a calorimeter; by taking into account the necessary precautions and corrections, the heat of combustion can be calculated from the rise in temperature of the water in the calorimeter, if the water value of the apparatus is known. In order to determine this quantity use is frequently made of "calibration substances", for which the heat of combustion is accurately known. For example, benzoic acid, the heat of combustion of which is 6315 gram-calories per gram, serves as a calibration substance.

From the molecular heat of combustion of a substance it is possible to calculate the heat of formation, *i.e.* the amount of heat, which should be set free (with exothermic compounds) or which should be added (with endothermic compounds), if the compound were produced from the elements. An example will make this clear.

The heat of combustion of carbon—in the form of graphite—amounts to 94.03 kcal. (per gram-atom) that of hydrogen 68.35 kcal. and that of methane 213 kcal.



from which it follows from HESS's law, that



From a knowledge of the heats of combustion it is also possible to calculate the heat effect of a chemical reaction; a direct determination is impossible in most organic reactions because of their slow rate.

CHAPTER 5

THE MAIN DIVISIONS OF ORGANIC CHEMISTRY

15. This book gives a survey of the most important groups of carbon compounds. These carbon compounds are divided into two main classes. This division is based on a theoretical concept, namely, the peculiarity in the structure of the molecules. Into the first class are collected those compounds, in which an open chain of atoms must be assumed to be present in the molecule; these carry the name of *aliphatic compounds* (or *fatty bodies*, Part One of this book). This name was introduced by A. W. VON HOFMANN because the animal and vegetable fats belong to this main class (*αλειφαρ*, fat).

The second main class contains those compounds, in which a closed chain of atoms must be assumed to be present in the molecule; these are therefore referred to as *cyclic compounds* (*κυκλος*, circle). They have been subdivided into *Carbocyclic compounds* (the closed chains consisting of C-atoms only, Part Two of this book) and *Heterocyclic compounds* (the closed chains containing also atoms other than carbon, Part Three of this book).

The significance of these concepts of "open" or "closed chains of atoms" will be explained later.

PART ONE
ALIPHATIC COMPOUNDS

CHAPTER 6

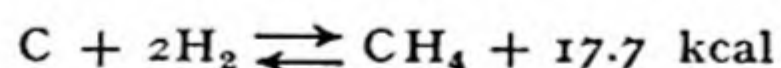
THE SERIES OF SATURATED HYDROCARBONS OR ALKANES

16. The first member of this series is *methane*, CH_4 , which may be regarded as the parent from which all aliphatic compounds are derived. Then follow *ethane* C_2H_6 , *propane* C_3H_8 , *butane* C_4H_{10} , *pentane* C_5H_{12} , *hexane* C_6H_{14} , etc., *pentatriacontane* $\text{C}_{35}\text{H}_{72}$, *hexacontane*, $\text{C}_{60}\text{H}_{122}$. These formulae can be summarised in the general expression $\text{C}_n\text{H}_{2n+2}$.

Nomenclature. The hydrocarbons $\text{C}_n\text{H}_{2n+2}$ are denoted by the termination "ane". The first four terms have special names, the remainder are named after the Greek or Latin numeral expressing the number of carbon atoms in the particular compound. Thus C_8H_{18} is called *octane*, $\text{C}_{12}\text{H}_{26}$ *dodecane*, $\text{C}_{31}\text{H}_{64}$ *hentriacontane*, etc. The general name for this group of hydrocarbons is the *alkanes*. They are spoken of as *saturated hydrocarbons* because these compounds are saturated with regard to hydrogen, *i.e.* they can no longer take up hydrogen atoms into their molecules. They are also called *paraffins*, derived from *parum affinis* (literally: but slightly responsive, *i.e.* in chemical reactions).

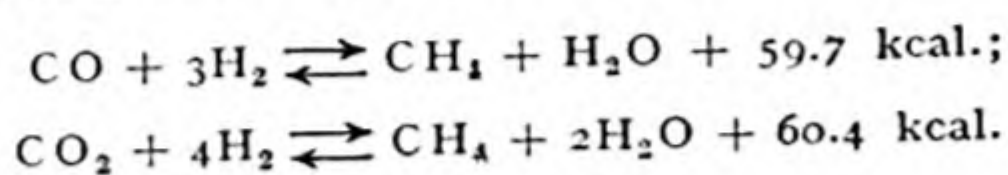
Frequently it is necessary to denote atomic groupings of the composition $\text{C}_n\text{H}_{2n+1}$. The general name for this is *alkyl* group, the particular name being derived by altering the termination *ane* of the appropriate hydrocarbon to *yl*; CH_3 is called *methyl*, C_2H_5 *ethyl*, C_3H_7 *propyl*, C_4H_9 *butyl*, $\text{C}_{12}\text{H}_{25}$ *dodecyl*, etc.

Methods of formation of methane. This gas is produced by direct synthesis from its elements, namely, by leading hydrogen over pure carbon at $1000\text{--}1200^\circ\text{C}$. Only a little methane is formed at these temperatures, since the equilibrium concentrations of the reaction

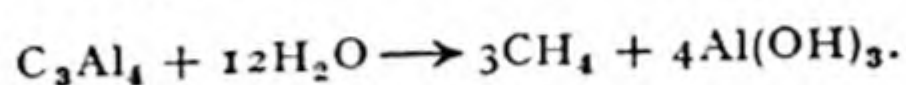


lie at 0.6 % CH_4 at 1100° and at 1.1 % CH_4 at 1000° (BONE, COWARD). At lower temperatures the reaction can be brought about by making use of the catalytic action of finely divided nickel. When hydrogen is passed over finely divided nickel covered with a thin layer of finely divided carbon at 550° , the exit gas contains 41 % of methane when equilibrium is reached

(SCHEFFER). The catalytic action of finely divided nickel in reactions, in which gaseous hydrogen has a reducing action, was discovered by SABATIER and SENDERENS. These investigators found that carbon monoxide and carbon dioxide could be easily reduced by gaseous hydrogen at 250° and 300°, respectively, to methane, if the gaseous mixture were passed over finely divided nickel (obtained from the oxide by reduction):



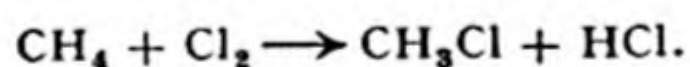
For the preparation of methane in the laboratory, use is made of the decomposition of aluminium carbide by water:



Methane made in this way is impure. For another method of preparation see 53 and 54.

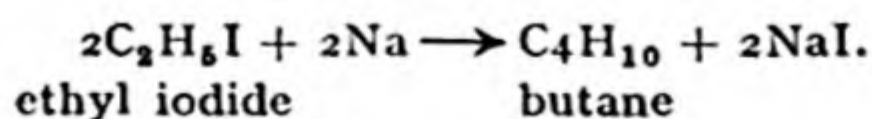
Methane is produced also by the thermal decomposition of coal (carbonisation); hence coal-gas contains 20–30 % of this hydrocarbon.

17. Physical and chemical properties of methane. It is an odourless and colourless gas; spec. grav. 0.559 (air = 1), critical pressure 55 atmospheres, critical temperature -82° , boiling point -162° , melting point -183° . It is very slightly soluble in water and rather more soluble in alcohol. Methane is unstable at temperatures above 1200° : it is decomposed into carbon and hydrogen by an electric arc or by induction sparks. It burns with a slightly luminous flame. Mixtures of methane with air or oxygen are explosive if the ratio between methane and air (oxygen) lies within certain limits (fire damp explosions). Chlorine or bromine react with methane; the hydrogen atoms are then replaced by chlorine or bromine, respectively, and hydrogen halide is produced at the same time:

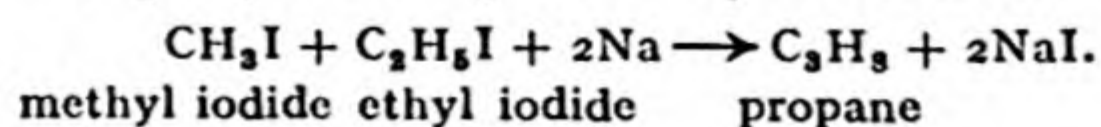


Replacement of one atom by another is termed *substitution*. If chlorine or bromine is present in excess, then a mixture of substitution products, viz. CH_3Cl , CH_2Cl_2 , CHCl_3 and CCl_4 , is produced. CCl_4 or CBr_4 , however, is the final product.

Preparation of homologues of methane. These may be prepared by treating alkyl iodides or alkyl bromides in ethereal solution with sodium (A. WURTZ, 1855):



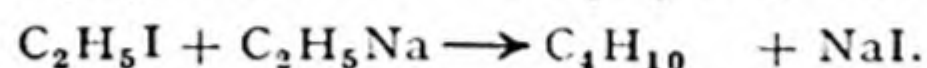
Propane could be prepared by this synthesis as follows:



In this reaction 2 molecules of CH_3I will react with sodium with the formation of *ethane*, while *butane* will be produced from 2 molecules of $\text{C}_2\text{H}_5\text{I}$. In general, three different alkanes are produced in the WURTZ reaction when two different alkyl iodides or bromides are used (for other syntheses of alkanes see 53, 54 and 39).

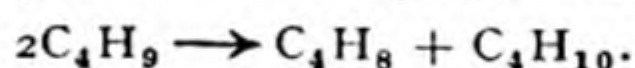
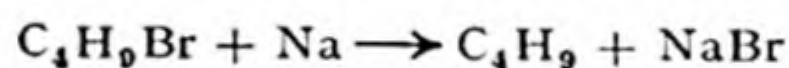
In principle, the homologues of methane can be prepared from this hydrocarbon by reacting it with bromine, preparing ethane from the methyl bromide so obtained, converting this to ethyl bromide, and so on.

Probably a molecule of sodium alkyl (53) is first formed in the WURTZ synthesis, which then reacts rapidly with another molecule of alkyl iodide:



When lithium is used instead of sodium, in some cases a lithium alkyl, for example, CH_3Li , can be isolated, since this compound reacts less rapidly with an alkyl iodide than does a sodium alkyl. This is strong support for the opinion mentioned above.

Besides the longer chained higher alkanes, in many cases there are produced as by-products in the WURTZ synthesis, alkanes and alkenes containing the same number of carbon atoms as the alkyl iodides used as starting materials. Thus *butene* and *butane* are also formed in the preparation of *n-octane* from *n-butyl* bromide. This must probably be explained by the intermediate production of the free radical (89) *butyl* from *butyl* iodide and sodium, which is then converted into *butene* and *butane*:



18. Homologous series. When the members of the series of saturated hydrocarbons are considered, it is seen that the difference in composition between any two compounds is represented by a multiple of the group CH_2 . These hydrocarbons show a great similarity in chemical properties.

Many groups of organic compounds are known in which the composition differs only in respect of the number of CH_2 groups in the molecule, and which show great similarity in chemical properties. Such compounds are said to be homologous (from $\delta\mu\lambda\omicron\gamma\omicron\sigma$ -corresponding); such a group is called a *homologous series*.

The principle of homology greatly simplifies the study of organic chemistry. The general chemical properties, which are essentially identical for all terms of the homologous series, can then be learned, instead of the properties of each compound separately. If the chemical properties of a number of the members of a series are known, it is even possible to forecast the most important properties of the other members of the series with certainty. Besides the general properties, each compound still has its individual chemical properties which will be mentioned in this text-book only if there is some particular reason for doing so. The physical properties of the members

of a homologous series gradually alter as the number of carbon atoms increases; this holds, for example, for melting points and boiling points, which increase in general as the series is ascended (see Table 6 on p. 49).

19. Isomerism and structure. Only one substance is known having the formula CH_4 , one compound of formula C_2H_6 and similarly one having the formula C_3H_8 . Two hydrocarbons, both having the molecular formula C_4H_{10} , namely, butane boiling at 0.6° and *isobutane* or 2-methylpropane with a boiling point of -10.2° , are known, however. Similarly, three hydrocarbons of formula C_5H_{12} are known and five of formula C_6H_{14} . The number of hydrocarbons, having the same molecular formula, increases rapidly the higher one rises in the homologous series.

This phenomenon of different compounds having the same molecular weight and the same percentage composition, is called *isomerism*. Such compounds are termed *isomers*, derived from *ἴσος*: equal and *μέρος*: part. (BERZELIUS).

The first example of isomerism was discovered in 1823, when GAY LUSSAC and, about the same time, LIEBIG and WÖHLER analysed the silver salts of fulminic and isocyanic acids and found the same composition for these substances notwithstanding that their properties were very different. Silver fulminate is explosive but silver isocyanate is stable. (Cf. 155 and 157).

Theory of structure. The phenomenon of isomerism was explained by a theory put forward in principle round about 1860 by COUPER and by KEKULÉ and later developed further by various investigators. In this *theory of chemical structure* a definite, unalterable arrangement is allotted to the atoms in the molecule of an organic compound. If the arrangement of the atoms in a molecule continually changes there can be no question of isomerism. It is impossible to see how the four atoms of carbon and the ten atoms of hydrogen in butane, for example, can give rise to two different substances, if the arrangement of these 14 atoms is not fixed, or what amounts to the same thing, if every arrangement is possible and all these configurations very rapidly pass over into one another by each atom being able to take up another position. Indeed, considering the very large number of molecules involved in every chemical experiment, then in any particular quantity of butane at any particular moment and under all conditions, all possible arrangements would occur and all these configurations would be present, always in unchanging quantities. In order to explain the phenomenon of isomerism it is necessary to assume that the atoms in complicated molecules can be arranged only in a limited number of quite definite ways, and that these configurations are not interconvertible under the conditions of the experiment. The difference in properties between isomeric

compounds can then be reduced to a difference in the arrangement of the same number of atoms.

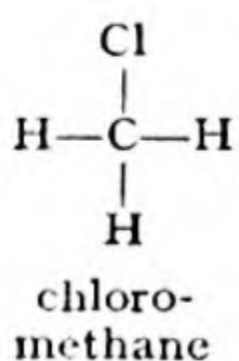
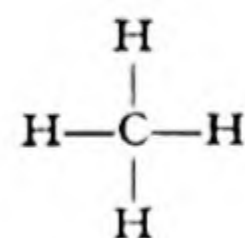
This idea was already discussed by various investigators in the first half of the 19th century, but could only be developed when the idea of valency or combining power had assumed a definite form.

Tetravalency of carbon. In by far the greater majority of carbon compounds carbon behaves as a tetravalent element. This is apparent from the composition of a number of compounds containing only one carbon atom, such as CH_4 , CCl_4 , CBr_4 and CO_2 . Investigation of more complicated carbon compounds has shown that in almost all of these compounds the carbon atoms are also tetravalent. One substance is known in which carbon is definitely bivalent, namely, the simplest carbon compound, carbon monoxide, and a few more complicated compounds in which one of the carbon atoms is considered to be bivalent, are also known (see 56). Compounds have also been discovered in which carbon is trivalent, but these substances have peculiar properties, as will appear later (see 89).

On the other hand, substances have never been found in which a higher valency than four must be ascribed to the carbon atom.

The idea that carbon is tetravalent occurred about the middle of the last century to various investigators: FRANKLAND, KOLBE, COUPER, KEKULÉ, and the last named especially took the tetravalency of carbon as the starting point for the classification of organic compounds.

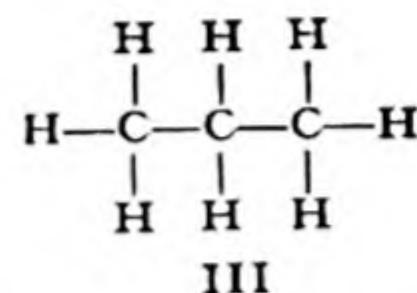
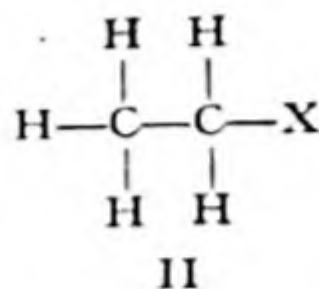
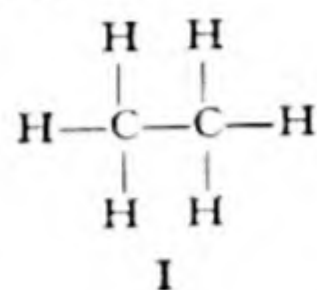
The arrangement of the atoms in the methane molecule can be represented by the annexed figure, each of the four valencies of the carbon atom—shown by a short straight line—being attached to one monovalent hydrogen atom. The hydrogen atoms cannot be mutually connected because each of the hydrogen atoms is provided with only one valency which is already joined with one of the valency bonds of the carbon atom. If a hydrogen atom in



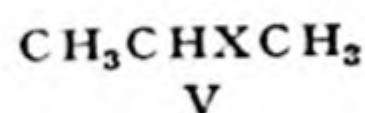
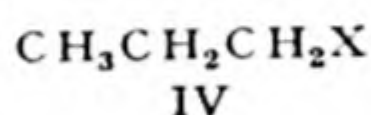
methane is substituted by a chlorine atom, chloromethane is produced. Only one compound is known with the formula CH_3Cl , which is in agreement with there being one tetravalent carbon atom, one monovalent chlorine atom and three monovalent hydrogen atoms, which can be arranged in the molecule in one way only.

Similarly, only one compound is known with the composition CH_3Br and only one CH_3I . In the synthesis of ethane by the method of WURTZ (17) the iodine atom in methyl iodide is replaced by the group CH_3 , which originates in a second molecule of methyl iodide. The arrangement of the atoms in a molecule of ethane must therefore be represented by two CH_3 groups joined together by a bond between the two carbon atoms (formula I).

Just as only one halogenomethane is known, only one mono-halogenated derivative of ethane is known. Indeed for a substance with the formula C_2H_5X (X is halogen) only one arrangement (II) of the atoms in the molecule is possible.



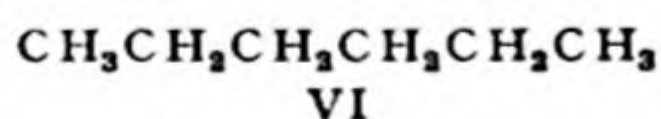
If sodium is allowed to react on a mixture of iodoethane and iodomethane, propane is produced; the molecule of this substance must therefore be represented by figure III or more briefly by: $H_3CCH_2CH_3$. Now the substitution of a hydrogen atom by a halogen atom in propane may be considered as taking place in two different ways. The halogen atom may be attached to either one of the terminal carbon atoms (IV) or to the middle carbon atom in the propane molecule (V):



The arrangement of the atoms is different in the two figures; it is impossible to work out a third arrangement for a compound of formula C_3H_7X . Thus if the isomerism is caused by a difference in the arrangement of the atoms in the molecule, *two and not more than two* isomeric compounds of the formula C_3H_7Cl , and likewise two and not more than two substances C_3H_7Br , etc., can exist. This conclusion is in agreement with the facts. The compound $CH_3CH_2CH_2I$ is named *1-iodopropane* or *n-propyl iodide*, the compound CH_3CHICH_3 is *2-iodopropane* or *isopropyl iodide*. The structures of 1-iodopropane and 2-iodopropane are deduced from their relationship with *n*-propyl alcohol and *isopropyl* alcohol, respectively. (Cf. 28 and 33).

We will now consider an example of how the structure of isomeric hydrocarbons from the series of alkanes can be determined. Amongst the five known hexanes is one which boils at 69° and another with a boiling point of 58° .

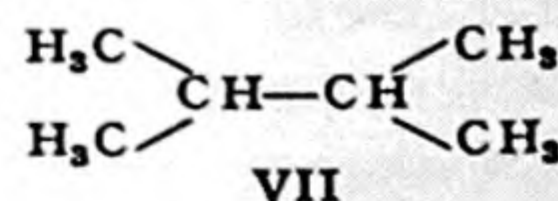
The former substance is obtained by allowing sodium to react with normal propyl iodide, $CH_3CH_2CH_2I$. Hence the structure VI must be ascribed to the *hexane* boiling at 69° .



The hexane with the boiling point of 58° is formed by the action of sodium on *isopropyl* iodide, CH_3CHICH_3 .

On these grounds the hexane is given the structure VII.

Thus in this reasoning it is assumed that both the



arrangement in the propyl group, $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—}$, present in the normal propyl iodide, and the arrangement in the *isopropyl* group, $\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH—} \\ \diagup \\ \text{CH}_3 \end{array}$, from the *isopropyl* iodide, remain intact in the formation of the above-mentioned hexanes.

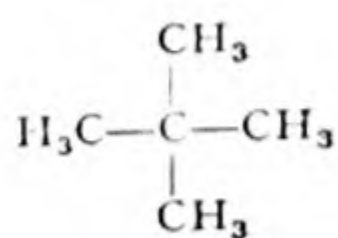
A priori it would not be inconceivable that in the action of sodium on propyl iodide or *isopropyl* iodide, not only is the bond between carbon and iodine broken but at the same time a rearrangement of the atoms occurred in the rest of the molecule, so that the same hexane might be obtained from either of the propyl iodides. Thus, for example, the *isopropyl* group would then be transformed into a *n*-propyl group. For this transformation to occur it would be necessary for a bond between a hydrogen atom and a terminal carbon atom to be broken and a bond between a middle carbon atom and a hydrogen atom to be formed.

The formation of hexane from *isopropyl* iodide would then be less simple than that from normal propyl iodide, since in the former case, besides the bond between the carbon and the iodine atom a bond between the carbon and the hydrogen atom must also be broken and a new bond between C and H must be produced. *The hypothesis lying at the basis of all determinations of structure is now this, that in the reactions under consideration the number of atom bonds which are broken is as small as possible.* The correctness of this hypothesis can only be apparent in an indirect way, namely, in that no experimental facts have yet been found which are at variance with the assumption made. Therefore, where possible, attempts will be made to derive the structure of a particular compound by different syntheses or reactions.

20. Carbon chains. In the foregoing paragraphs it is explained, that in a molecule of propane an arrangement of three carbon atoms joined with one another, must be assumed, while in a molecule of hexane a series of six carbon atoms joined with each other occurs. Such groupings of mutually connected carbon atoms are called *carbon chains*. Compounds are now known containing in their molecules a large number of carbon atoms joined in a chain. A hydrocarbon of the formula $\text{C}_{62}\text{H}_{126}$ (dohexacontane), for example, is known in which a chain of sixty two carbon atoms occurs. Such alkanes with a large number of carbon atoms are stable compounds at ordinary temperature. The property of forming chains of atoms is characteristic of carbon atoms; this property is absent or present in a much lesser degree in atoms of other elements. Experience has shown that a bond between two carbon atoms is difficult to break; this is especially so for the carbon bonds in saturated hydrocarbons and also for many other groups of compounds containing carbon chains in their molecules.

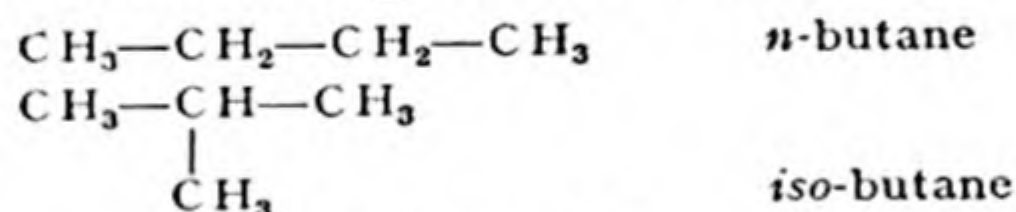
Normal carbon chains. A carbon chain such as occurs in hexane of boiling point 69° (VI) is called a *normal chain*. Hence this hexane is called normal hexane or *n*-hexane. In a normal chain, each of the *terminal* carbon atoms is bound to one other carbon atom, the remaining carbon atoms on the other hand are joined to two carbon atoms.

Branched carbon chains. The hexane of boiling point 58° (VII) is an example of this type of compound. In this case two carbon atoms are present each of which are joined to three other carbon atoms. A carbon atom which is attached to only one other carbon atom is called a *primary*, if it is joined to two other carbon atoms a *secondary*, and when it is attached to three other carbon atoms it is termed a *tertiary* carbon atom. Finally, a carbon atom may be combined as a *quaternary* atom as in the pentane of the annexed structure.



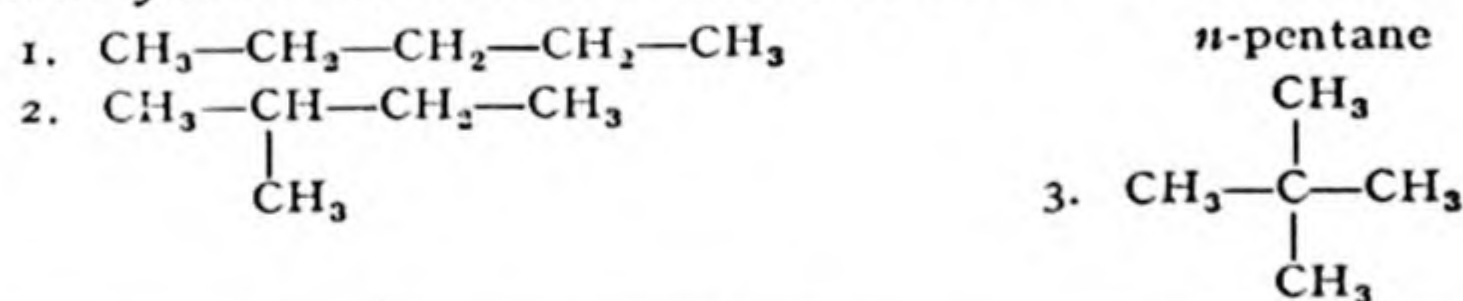
Compounds with one or more tertiary carbon atoms in the molecule are frequently denoted by the prefix *iso*.

21. Number of possible isomers. On the basis of the two premises, the tetravalency of carbon and the formation of carbon chains, it is possible to predict how many isomeric hydrocarbons of a given composition, $\text{C}_n\text{H}_{2n+2}$, are possible. Two arrangements are possible for a compound of the composition C_4H_{10} :



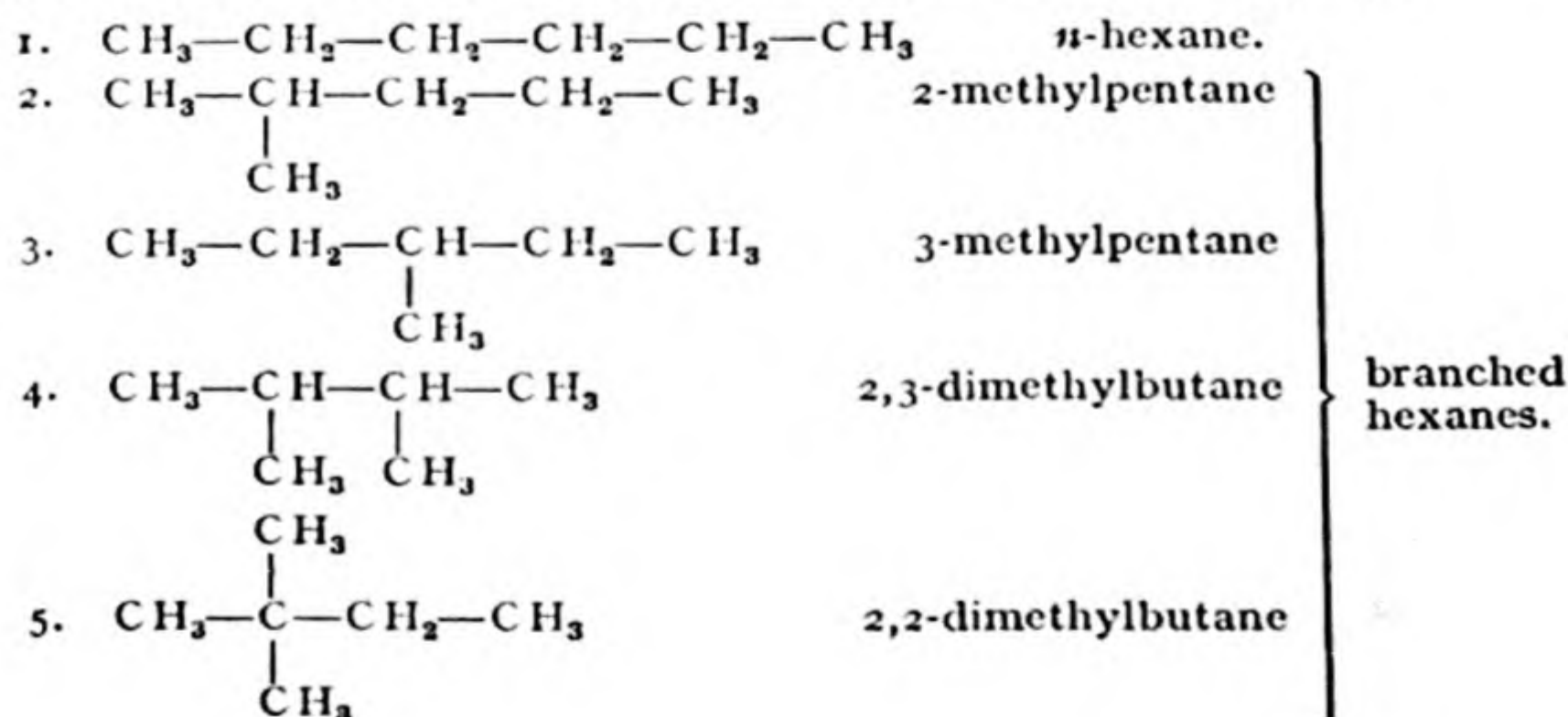
A third possibility does not exist in this case.

Three *structural formulae* can be set out for a substance C_5H_{12} .



branched pentanes.

while five isomers can be formulated for hexane C_6H_{14} :



Thus it follows from the theory of structure that it will be possible to prepare five and not more than five isomeric hexanes, or three isomeric pentanes or two isomeric butanes. If it should prove actually possible to obtain the number of isomers which is predicted in a particular case by the theory, and if moreover it is not possible to prepare more isomeric compounds than the theory will allow, it is very probable that the hypotheses on which the theory of structure rests, are correct. Indeed, it has now been established in the examples mentioned above and in a large number of other cases, that the number of isomers is always in agreement with what the theory of structure would lead one to expect.

The number of isomers theoretically possible increases rapidly as the molecule of the compound under consideration contains more carbon atoms. According to calculations by BLAIR and HENZE there are 9 possible isomers of the hydrocarbon C_7H_{16} , 18 of C_8H_{18} , 35 of C_9H_{20} , 75 of $C_{10}H_{22}$, 4347 of $C_{15}H_{32}$, and 366,319 of $C_{20}H_{42}$, not including stereoisomers.

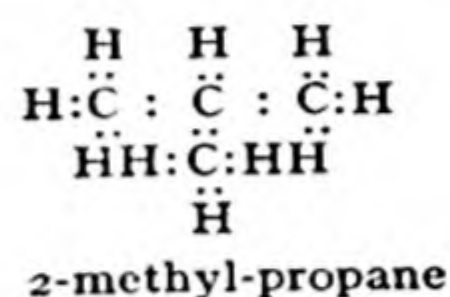
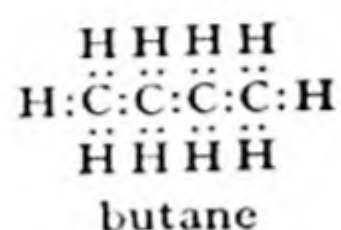
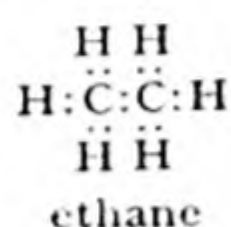
In such cases the number of isomers which have actually been prepared is much smaller than the number of isomers theoretically possible. For example, no attempt has been made to prepare all the 4347 isomeric hydrocarbons of formula $C_{15}H_{32}$, since the conclusions of the theory of structure can be tested in a much simpler manner and no new discoveries are likely to follow from such an investigation. It is not to be doubted that it would, in principle, be quite possible to prepare all the isomers in such a case.

22. Nomenclature of isomeric alkanes. For hydrocarbons with normal carbon chains the nomenclature is simple; they are denoted by the prefix *n*. The following rules are valid for the nomenclature of hydrocarbons with branched chains: the longest normal chain occurring in the molecule is chosen as the main chain, from which the name is derived. The various carbon atoms in this chain are now indicated by a number; the position of the side-chain is given by the number of the carbon atom in the main chain to which the side-chain is attached. Examples of these rules are to be found in the names of the branched chain hexanes (see p. 46).

Electronic formulae. The bond between two carbon atoms, like the bond between a carbon atom and a hydrogen atom, is a *homopolar* or *covalent* bond. A homopolar bond comes into being by the "sharing" of two electrons with opposite spins. Each of the four homopolar bonds in methane is produced therefore by one of the four valency electrons from the outer shell of the carbon atom forming an electron pair with the valency electron of a hydrogen atom. Hence the molecule of methane can be expressed by the following electronic formula, in which the electrons of the outermost shell are repre-

sented by dots; the letters C and H represent the "atom-shells" of carbon and hydrogen (proton).

Each electron pair belongs both to the carbon atom and to a hydrogen atom; this is expressed in such a way that the carbon atom shares a pair of electrons with a hydrogen atom four times, so that the carbon atom may be considered as having eight electrons—an *electron octet*—in its outermost shell. In the same way electronic formulae can be drawn for the homologues of methane (octet theory of G. N. LEWIS and I. LANGMUIR).



It is seen that each of the carbon atoms has eight electrons (*octet*) and each hydrogen atom two electrons (*doublet*) in the outermost shell. It is clear that this octet theory leads to the same conclusions as regards the phenomenon of isomerism as the formal theory of structure, in which the nature of the bonding-forces was left undetermined, since the electronic formulae also are based on the tetravalency of the carbon atom, which possesses four valency electrons, and the monovalency of the hydrogen atom, which has one valency electron. From this it follows that all the alkanes have an *even number* of valency electrons.

23. Physical properties of the alkanes. Table 6 gives the boiling points, melting points and specific gravities of a number of alkanes with normal carbon chains.

From this table it appears that the differences in the melting points and boiling points between successive members of the series become smaller as the number of carbon atoms increases. This is a general phenomenon in homologous series.

On comparing the boiling points of isomeric alkanes, it is seen that the compound with the normal carbon chain has the highest boiling point.

Isomeric pentanes:		b.p.
<i>n</i> -pentane	CH ₃ CH ₂ CH ₂ CH ₂ CH ₃	35.9°
2-methylbutane	CH ₃ CHCH ₂ CH ₃ CH ₃	27.8°
2,2-dimethylpropane	CH ₃ CH ₃ CH ₃ CCH ₃ CH ₃	9.5°

Isomeric octanes:		b.p.
<i>n</i> -octane	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	125.8°
4-methylheptane	$\text{CH}_3\text{CH}_3\text{CH}_2\underset{\text{CH}_3}{\text{CH}}\text{CH}_2\text{CH}_2\text{CH}_3$	118°
3-methylheptane	$\text{CH}_3\text{CH}_2\underset{\text{CH}_3}{\text{CH}}\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	119°
2-methylheptane	$\text{CH}_3\underset{\text{CH}_3}{\text{CH}}\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	117.2°
2,5-dimethylhexane	$\text{CH}_3\underset{\text{CH}_3}{\text{CH}}\text{CH}_2\text{CH}_2\underset{\text{CH}_3}{\text{CH}}\text{CH}_3$	109.2°
2,2,3,3-tetramethylbutane	$\begin{array}{c} \text{CH}_3\text{CH}_3 \\ \quad \\ \text{CH}_3\text{C}-\text{C}-\text{CH}_3 \\ \quad \\ \text{CH}_3\text{CH}_3 \end{array}$	106.5°

It is seen also that the boiling point is lower the more branches there are in the chain.

TABLE 6
SOME PHYSICAL CONSTANTS OF ALKANES

Name	Formula	Melting point	Boiling point	Spec. grav.	Mol. heat of combustion gas phase <i>p</i> const.
Methane	CH_4	—182.6°	—161.6°	0.4240 (b.p.)	212.8
Ethane	C_2H_6	—172.1°	— 88.5°	0.5462 (b.p.)	372.8
Propane	C_3H_8	—187.1°	— 42.5°	0.5824 (b.p.)	530.6
Butane	C_4H_{10}	—138.3°	— 0.5°	0.5788 (20°)	687.9
Pentane	C_5H_{12}	—129.7°	35.95°	0.6262 (20°)	845.3
Hexane	C_6H_{14}	— 95.5°	68.75°	0.6594 (20°)	1002.4
Heptane	C_7H_{16}	— 90.8°	98.40°	0.6837 (20°)	1159.4
Octane	C_8H_{18}	— 56.8°	125.8°	0.7028 (20°)	1316
Nonane	C_9H_{20}	— 53.8°	150.7°	0.7181 (20°)	1473.4
Decane	$\text{C}_{10}\text{H}_{22}$	— 29.7°	174°	0.7298 (20°)	1630.4
Undecane	$\text{C}_{11}\text{H}_{24}$	— 25.6°	195.8°	0.7404 (20°)	
Dodecane	$\text{C}_{12}\text{H}_{26}$	— 9.6°	216.2°	0.7493 (20°)	
Tetradecane	$\text{C}_{14}\text{H}_{30}$	5.5°	251°	0.7636 (20°)	
Hexadecane	$\text{C}_{16}\text{H}_{34}$	18°	280°	0.7749 (20°)	
Eicosane	$\text{C}_{20}\text{H}_{42}$	36.4°	309.7°	0.7777 (m.p.)	
Heneicosane	$\text{C}_{21}\text{H}_{44}$	40.4°	215 at 15 mm.	0.7783 „	
Tricosane	$\text{C}_{23}\text{H}_{48}$	47.4°	234 „ „ „	0.7797 „	
Hentriacontane	$\text{C}_{31}\text{H}_{64}$	68.1°	302 „ „ „	0.7808 „	
Pentatriacontane	$\text{C}_{35}\text{H}_{72}$	74.7°	331 „ „ „	0.7816 „	
Hexacontane	$\text{C}_{60}\text{H}_{122}$	99°	250 „ 10 ⁻⁵ „		

The *molecular heat of combustion* is practically additive in the normal alkane series if the first few members are ignored. For a number of normal alkanes with more than five carbon atoms the molecular heat of combustion, calculated on the gaseous substance at constant pressure, can be represented by the formula: molecular heat of combustion = $60.40 + n(157.00 \pm 0.08)$ kg cal., in which n is the number of carbon atoms in the molecule (ROSSINI).

Hydrocarbons with branched chains have a smaller heat of combustion than the isomers with normal chains; the differences are small however.

The *molecular refraction* is an additive property in homologous series as was first shown by EYKMAN. Usually the first few members at the beginning of the homologous series must be left out of consideration, because for these compounds the increase in the molecular refraction per CH_2 -group is not constant. According to concordant observations made by WIBAUT and co-workers and by SHEPARD, HENNE and MIDGLEY the increase in the molecular refraction is constant within the errors of observation for the normal alkanes containing from 5 to 16 carbon atoms.

TABLE 7
MOLECULAR REFRACTION

Normal alkane	$\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d}$	ΔCH_2 for $\lambda = 5893$ sodium D-line at 20°
C_5H_{12}	25.26	
C_6H_{14}	29.88	4.62
C_7H_{16}	34.53	4.65
C_8H_{18}	39.16	4.63
C_9H_{20}	43.80	4.64
$\text{C}_{10}\text{H}_{22}$	48.45	4.65
$\text{C}_{11}\text{H}_{24}$	53.09	4.64
$\text{C}_{12}\text{H}_{26}$	57.74	4.65
$\text{C}_{16}\text{H}_{34}$	76.23	4×4.62

From Table 7 it appears that the most probable value for ΔCH_2 is 4.64. Small deviations from strict additivity occur with branched chain alkanes; thus for 2,3 dimethylpentane $\left[\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d} \right]_{5893}^{20^\circ} = 34.30$ a value which is therefore 0.23 lower than for normal heptane.

Ignoring such small deviations, the molecular refraction may be considered as additive in the group of alkanes.

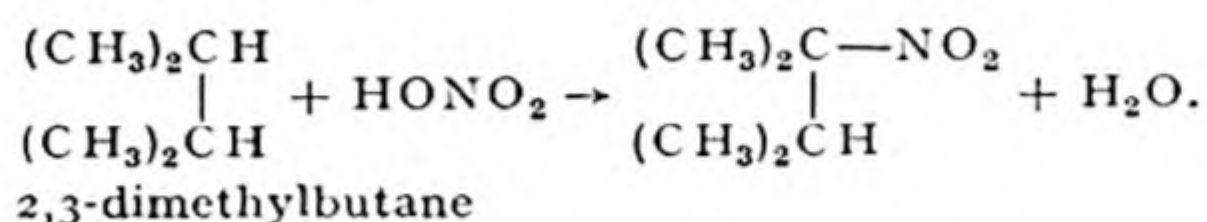
If $n \times 4.64$ is subtracted from the observed value for the molecular refraction for a hydrocarbon $\text{C}_n\text{H}_{2n+2}$, the value is found for the contribution made by two combined hydrogen atoms. If now this figure is subtracted from the value for the CH_2 -group the amount contributed by a combined C-atom is found. The refraction equivalents calculated in this way amount to 2.56 for carbon and 1.04 for hydrogen (both for $\lambda = 5893$).

The value of ΔCH_2 has been accurately determined also in other homologous series; from measurements carried out by BRUYLANTS on the series of normal alkane-carbonitriles from C_1 to C_{13} inclusive, it also follows that $(\Delta \text{CH}_2)_{5893}^{20^\circ} = 4.64$ (56). Later on we shall consider groups of compounds, in which the molecular refraction depends not only on the nature and the number of atoms but also to a marked extent

on the structure, so that the knowledge of this quantity can be a help in the determination of structure (cf. 84, 92, 100, 299).

24. Chemical properties of the alkanes. One or more of the hydrogen atoms in the alkanes may be easily substituted by chlorine or bromine (17). This reaction is greatly accelerated by light or by certain catalysts such as, for example, iodine. The alkanes with normal carbon chains do not react at ordinary temperatures with either concentrated nitric acid or concentrated sulphuric acid.

Alkanes with a hydrogen atom combined with a tertiary carbon atom may be nitrated by warming with nitric acid (KONOWALOW):



A dinitro-compound is also formed as well as oxidation products. According to recent investigations by HASS, nitro-alkanes are produced by the action of nitric acid vapour on propane, butane and other homologues at a temperature of 400°. Degradation of the carbon chain also occurs in this case; from propane there is produced a mixture of 1-nitropropane, 2-nitropropane, nitroethane and nitromethane. Nitroalkanes may be prepared in this way on a large scale.

In general, the alkanes are stable towards oxidising agents such as potassium permanganate, chromic acid, ozone, hydrogen peroxide, etc. at ordinary temperatures.

The higher alkanes (components of paraffin oil) can be oxidised by the action of air or oxygen at high pressure and about 150° with the formation of fatty acids (66) along with some hydroxy-acids.

In connection with combustion to carbon dioxide and water, which occurs when alkanes are brought to a sufficiently high temperature with excess air or oxygen and may take place explosively, partial oxidation occurs at temperatures below the ignition temperature.

Small quantities of formaldehyde (62) and formic acid (69) are formed along with H₂O, CO₂ and CO in the oxidation of methane at about 450°, with insufficient oxygen for complete combustion. Ethyl alcohol (31) is produced along with a little ethanal (63) and acetic acid (70) by heating a compressed mixture of ethane with a few percent of oxygen for a short time at 360° (BONE). Formaldehyde and acetaldehyde as well as hydrogen peroxide are produced amongst other things, by the slow combustion of propane at about 450°.

Isomerisation of alkanes. The transformation of alkanes with normal carbon chains into isomers with branched chains is very remarkable; these reactions, which take place slowly and are reversible, occur on heating

with aluminium chloride and hydrogen chloride, which act catalytically (IPATIEFF, GLAZENBROOK, SCHUIT *et al.*). In this way an equilibrium mixture containing about 70 % of *isobutane* is produced from *n*-butane at 100°. In the reaction *n*-pentane \rightleftharpoons 2-methylbutane, the equilibrium mixture at 80° contains about 87 % of the branched isomer. A mixture of the five isomeric hexanes is obtained on heating *n*-hexane with AlCl₃ and HCl at 80°.

The rule of even numbers of atoms

25. The number of hydrogen atoms in the alkanes is even, as appears from the general formula C_nH_{2n+2} . All other organic compounds—with a few exceptions—may be considered as having been produced: 1) by replacing the hydrogen atoms by other elements or groups of atoms, 2) by loss of an even number of hydrogen atoms 3) by causes 1 and 2 together. From this it follows that the sum of the atoms with odd valencies (hydrogen, halogens, nitrogen, phosphorus, etc.) in organic compounds must always be an even number. The molecule of a substance, the percentage composition of which agrees with the formula $C_3H_2O_2N$, must therefore be at least twice as large.

Some substances are known which form an exception to this rule, namely, hydrocarbons with an odd number of hydrogen atoms. A few nitrogen compounds are also known in which the sum of the hydrogen and nitrogen atoms is an odd number. These substances belong to the so called "free radicals". (89)

Occurrence of hydrocarbons C_nH_{2n+2} in nature. Mineral oil. Petroleum

26. Methane is produced by the decomposition of vegetable residues (cellulose) under the influence of bacteria and therefore forms the main constituent of marsh gas; methane is also set free from coal measures (fire damp). Higher members of the alkane series are met with in the form of waxy products in various essential oils; *n*-heptane occurs in the essential oil from an American pine (*P. sabiniana*) and is prepared from it.

By the dry distillation of bituminous brown coal, which is carried out at 500–600°, a tar is produced, in which a large proportion of alkanes is present besides homologues of phenol, and from which, amongst other things, solid paraffin is produced. This material contains the normal alkanes from $C_{16}H_{34}$ to $C_{36}H_{74}$.

Mineral oil or Petroleum consists of mixtures of a very large number of hydrocarbons; our knowledge of the components of these oils, especially as regards the higher boiling constituents, is still very incomplete. Practically all kinds of petroleum oil contain alkanes and cyclic hydrocarbons, both cyclanes (286), cyclopentane, cyclohexane and their homologues—usually called *naphthenes* in petroleum technology—and aromatic hydrocarbons. Very probably hydrocarbons with hydrogenated bicyclic ring-systems also occur in petroleum. Alkenes are not encountered in raw petroleum but occur in distillates produced at high temperatures. The ratio in which these groups of hydrocarbons occur differ very widely for oils of different origin.

The Pennsylvanian oils (North America) contain large amounts of alkanes, from

the highest to the lowest members of the series with both normal and branched carbon chains. The natural gases, which arise from the oil wells in some oil fields and in other places make their appearance in various strata, consist chiefly of methane along with ethane, propane, butane and *isobutane*. Russian oils (Baku, Caucasus) contain large amounts of naphthenes; Californian and Rumanian oils also are rich in cyclic hydrocarbons; oils from Java, Borneo or Sumatra contain considerable quantities of aromatics comprising only small amounts of benzene and toluene but more of their homologues; naphthalenes and mono- and di-methylnaphthalenes may be isolated from the kerosene distillates. Besides hydrocarbons, crude petroleum contains very small quantities of organic oxygen compounds, *e.g.* naphthenic acids (see 289) and sulphur compounds of unknown constitution and sometimes also small quantities of organic nitrogen compounds.

Very little is known of the way in which petroleum is produced. On the basis of geological and chemical considerations it is generally accepted that petroleum is produced from animal and/or vegetable remains. As chemical arguments for this supposition may be mentioned that optical activity has been observed in some petroleum fractions and that porphyrins occur (320), [both those related to chlorophyll (321) and those related to haemin], in different kinds of crude petroleum and in asphalt (TREIBS). From this it should follow that both the remains of chlorophyll-containing plants and of haemoglobin-containing animals have contributed to the formation of crude oil. The starting material from which petroleum is produced was probably formed from the dead remains of swimming flora and fauna (plankton) from inland seas.

Petroleum is brought to the surface from deep lying strata through bore holes and then submitted to fractional distillation. Both the distillates boiling over the range about 40° to 180° (benzine, petrol) and that from 180° to 300° (lamp oil paraffin or "kerosene"), are purified by treatment with concentrated sulphuric acid (followed by treatment with caustic soda and water), by which means impurities giving rise to the formation of resins are removed. Another method of purifying petroleum distillates (*e.g.* kerosene) consists in extracting with liquid sulphur dioxide, in which aromatic and unsaturated hydrocarbons are soluble and are therefore removed (EDELEANU).

Petroleum ether or light petroleum (40–70°), *benzine* or *petrol* (70–120°) and *ligroin* or white spirit (120–150°) are separated. Petroleum ether is also recovered from natural gases by condensation and by washing with a suitable petroleum fraction, as well as from the crude oil by distillation.

Propane and butane are also separated from natural gas to serve as gaseous fuels.

The fraction following the kerosene fraction (boiling to 350°) furnishes fuel oil for heavy motors (Diesel oil). The viscous liquid remaining behind after the removal of this fraction, is sometimes used as liquid fuel or worked up to various products such as *lubricating oil*, *petroleum asphalt* and *paraffin*.

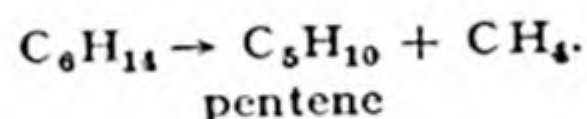
Petroleum oils consisting chiefly of naphthenes furnish viscous residues from which lubricating oils and greases are recovered by distillation with steam or by vacuum distillation. The fractions remaining behind after removing the lubricating oils are worked up for *petroleum asphalt* (*petroleum pitch*).

Good lubricating oils are also obtained from paraffinic petroleum oils containing large amounts of alkanes. Lubricating oils consist of mixtures of a large number of hydrocarbons; very little is known about the individual components. Moreover the question as to the relationship between lubricating properties and chemical constitution is still for the greater part unsolved.

In the working up of paraffinic oils, solid paraffin wax, which separates in a solid condition on cooling, is recovered from the distillate residues. This material consists of a mixture of alkanes with 20–35 (and possibly more) carbon atoms; Rangoon paraffin wax consists chiefly of alkanes with normal carbon chains. Paraffin wax is used in the manufacture of matches and candles amongst other things. *Vaseline*, a soft semi-solid mass and *paraffin oil* likewise consist of mixtures of alkanes.

Asphalt (ἀσφαλτος = unchangeable), which occurs in the asphalt lake in Trinidad and in various other places, consists of a mixture of hydrocarbons of high molecular weight and contains also compounds containing oxygen, sulphur and nitrogen: the chemical constitution of the constituents of asphalt is unknown. *Petroleum asphalt* is a material closely allied to the natural product: both materials are used for road making and for electrical insulation.

Since the quantity of petrol obtained by working up crude oil is much less than the quantity of higher boiling distillates and the need for petrol for automobile and aeroplane engines is so very great, processes have been developed by which mixtures of high-boiling hydrocarbons can be converted by thermal decomposition or “cracking” into hydrocarbons of lower molecular weight and therefore lower boiling point. The thermal decomposition of hexane in the gas phase at 600° takes place partly as follows:



A normal carbon chain can be split up in such a way that the homologues of methane are produced alongside one another.

Simultaneously fission also takes place thus: $\text{C}_n\text{H}_{2n+2} \rightarrow \text{H}_2 + \text{C}_n\text{H}_{2n}$ (alkene), and to some extent much more profound decomposition with the separation of carbon and hydrogen. In the thermal decomposition of hydrocarbon mixtures from mineral oil, unsaturated hydrocarbons are therefore produced, both aliphatic and cyclic (from cyclanes) as well as alkanes and hydrogen; a considerable amount of carbon also separates as *petroleum coke*. In the *Dubbs cracking process* the oil to be cracked is subjected in the liquid state to a temperature of about 500° under high pressure. *Petrol from the cracking process* contains a high percentage of unsaturated hydrocarbons, chiefly alkenes.

Petrol consisting mainly of alkanes with normal carbon chains is of little use in engines working at a high compression ratio (e.g. aeroplane engines), since a sudden rise in the rate of combustion occurs, which causes the engine to “knock”. It has been found that branched chain alkanes show less tendency to knock, i.e. they have better “antiknock properties”. In order to be able to give the antiknock rating of a petrol, its behaviour in an engine is compared with that of two reference substances: 2,2,4-trimethylpentane (b.p. 99.1°) called *iso-octane* in practice, and *n*-heptane (b.p. 98.4°) (EDGAR). To *iso-octane*, which has very good antiknock properties, an *octane number* of 100 is given by definition; *n*-heptane, which has very poor antiknock properties, has an octane number of 0. A petrol which shows the same behaviour in a testing engine specially constructed for this purpose as a mixture of 70 volumes percent. of *iso-octane* and 30 volumes percent. of *n*-heptane, has an octane number of 70.

Alkenes have a higher octane number than the corresponding alkanes with the same carbon chain; aromatic hydrocarbons also have a high octane number. Alkenes and alkanes with branched chains are prepared synthetically in order to obtain petrol

with a high octane number. The isobutene occurring in cracking gases can be polymerised with the aid of sulphuric acid (see 85) to a mixture of octenes consisting mainly of 2,4,4-trimethylpentene-1 and 2,4,4-trimethylpentene-2. 2,2,4-Trimethylpentane mentioned above, is obtained by the catalytic reduction of this mixture. The anti-knocking properties of petrol can be increased considerably also by the addition of a very small quantity of tetraethyl lead, which is therefore used as an "antiknock" agent. (MIDGLEY).

As far as is known, the supplies of mineral oil are much smaller than the coal deposits available for mining. Attempts have therefore been made to prepare mixtures of liquid hydrocarbons from coal to replace petrol and fuel oil.

In the BERGIUS process, powdered coal or brown coal slurried in a high boiling hydrocarbon oil is heated at about 450° under a hydrogen pressure of 150–200 atm. in presence of catalysts like molybdenum sulphide which are not poisoned by sulphur compounds. In this way the coal substance is decomposed with the absorption of hydrogen and is converted to a considerable extent into liquid hydrocarbons.

Another method, discovered by F. FISCHER and H. TROPSCH, starts from "water gas" obtained by the action of steam on red-hot coke and consisting chiefly of hydrogen and carbon monoxide. If a mixture of carbon monoxide and hydrogen is passed at ordinary pressure and at about 300° over certain catalysts consisting of, for example, finely divided iron or cobalt and a non-reducible oxide like alumina or magnesium oxide, a mixture of liquid hydrocarbons, chiefly alkanes, is produced. If the reaction is carried out with ruthenium as a catalyst, at a pressure of about 1000 atm., a mixture of alkanes with 1000 or more C-atoms per molecule is obtained. Hydrocarbons with such a high molecular weight have not so far been encountered in nature.

From these experiments it appears that the course of the reaction between CO and H_2 can be modified by using catalysts having very specific properties. Indeed by using pure nickel as the contact substance, the reduction of carbon monoxide with molecular hydrogen takes such a course that methane and water are the sole products. It is not yet clear how the formation of the homologues of methane in the experiments of FISCHER and TROPSCH is to be explained; perhaps metal carbides are formed by the action of CO on the metal of the contact mass and these carbides are then decomposed by hydrogen into metal and hydrocarbons.

CHAPTER 7

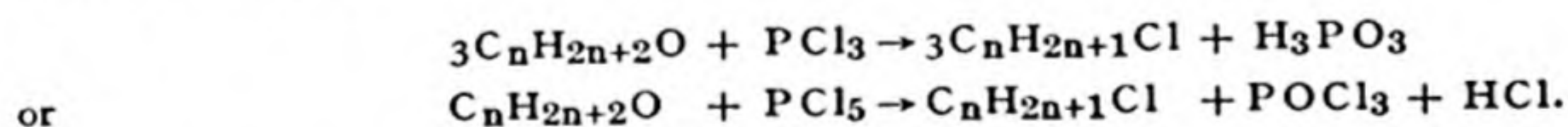
COMPOUNDS WITH ONE CHARACTERISTIC ATOM OR GROUP OF ATOMS

27. In the following we shall discuss a number of classes of compounds all of which are characterised by having in the molecule one characteristic atom—a halogen atom—or one characteristic group of atoms. The characteristic group—also called the *functional group*—may be, for example, a hydroxyl-group —OH , an alkoxy-group $\text{—OC}_n\text{H}_{2n+1}$, a cyano-group —CN , an amino-group —NH_2 , an aldehydo-group —CHO or a carboxyl-group —COOH . All these compounds may be considered as having been derived from alkanes by substitution.

(i) ALKANOLS (ALCOHOLS) $\text{C}_n\text{H}_{2n+2}\text{O}$

28. The members of this homologous series satisfy the general formula $\text{C}_n\text{H}_{2n+2}\text{O}$; they are named after the corresponding hydrocarbons by adding the suffix *ol*: methanol CH_4O , ethanol $\text{C}_2\text{H}_6\text{O}$, two isomeric propanols $\text{C}_3\text{H}_8\text{O}$, four isomeric butanols $\text{C}_4\text{H}_{10}\text{O}$, the pentanols $\text{C}_5\text{H}_{12}\text{O}$, etc.

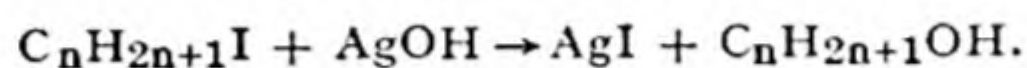
Structure and methods of formation. When an alcohol is treated with phosphorus tri- or penta-chloride, a molecule of alkyl chloride is produced from a molecule of alcohol:



In this reaction an oxygen atom and a hydrogen atom together are replaced by a chlorine atom. The monovalent chlorine atom in the $\text{C}_n\text{H}_{2n+1}\text{Cl}$ so formed is attached to a carbon atom of the alkyl group $\text{C}_n\text{H}_{2n+1}$ by one valency bond. Therefore, in the alcohol $\text{C}_n\text{H}_{2n+2}\text{O}$, the alkyl group $\text{C}_n\text{H}_{2n+1}$ is combined with a monovalent group containing an oxygen atom and a hydrogen atom, which can be none other than the group —O—H ; the structure of an alcohol must be represented therefore by the formula $\text{C}_n\text{H}_{2n+1}\text{—O—H}$. When sodium is allowed to react on an alcohol, $\text{C}_n\text{H}_{2n+2}\text{O}$, 1 gram-atom of hydrogen is set free from 1 gram-molecule of alcohol, and a compound $\text{C}_n\text{H}_{2n+1}\text{ONa}$, called a *sodium alcoholate*, is produced. Hence, in the alcohol-molecule, one hydrogen atom is present which can be replaced

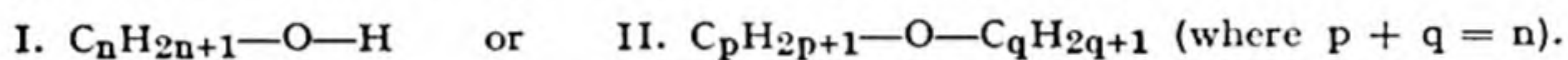
by an atom of sodium (or another alkali metal). It is permissible to assume that this is the hydrogen atom combined with oxygen, since hydrogen is also liberated by sodium from water—for the molecule of which no other structure is possible than H—O—H .

The supposition of the presence of a hydroxyl group in the molecule of the alkanols is in agreement with a general method of formation from alkyl halides, particularly from alkyl iodides, by treatment with moist silver oxide. It is usually assumed that a small quantity of silver hydroxide, to which the structure Ag—O—H is ascribed, dissolved in water, is present in this reagent. The formation of alkanol can therefore be represented thus:



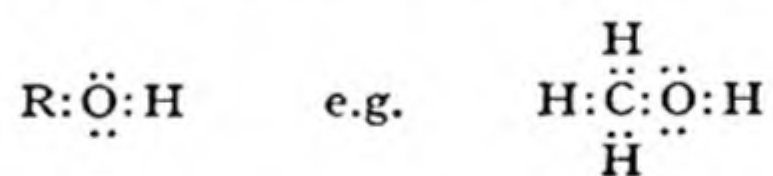
The halogen atoms in alkyl chlorides or bromides can also be replaced by hydroxyl groups; this can be brought about in some cases by heating with water or with high temperature steam.

The structure of the alcohol may be derived by still another method of reasoning. Assuming that the H-atoms are monovalent, the O-atom bivalent and the C-atoms tetravalent, in a compound of the composition $\text{C}_n\text{H}_{2n+2}\text{O}$ the oxygen atom can be combined in two ways only:



It is clear that the structure of an alkanol cannot be represented by formula II: all the hydrogen atoms in this structural formula are attached directly to carbon, so that the formula can give no account of the properties or the methods of formation of the alcohols.

The electronic structure of the alcohols is given in the following formulae

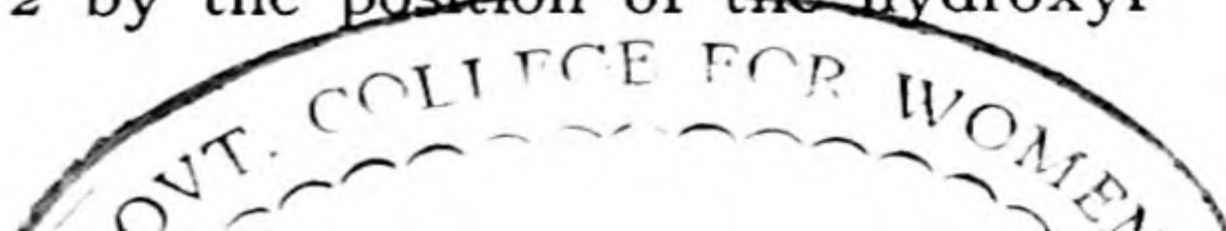


The oxygen atom has six electrons in the outer shell: of these, two are used for the formation of pairs of electrons with the available valency-electrons of the alkyl group and of the hydrogen atom; these pairs of electrons bring about the combination between R and O, and H and O, respectively. The oxygen atom still has two remaining pairs of electrons which do not take place in chemical combination; these are known as *lone pairs of electrons*.

The formation of alcohols from alkyl halides is of importance as a method of preparation in a few cases only; frequently the alkyl halides are prepared in just the opposite way from the corresponding alcohols (see 39).

Other general methods of making alkanols will be discussed later (59).

Isomerism and nomenclature. Isomerism can occur in the alcohol group: 1 by branching in the carbon chain, 2 by the position of the hydroxyl



group 3 by the causes mentioned in 1 and 2 working together. The position of the hydroxyl group is indicated by the number of the carbon atom to which it is attached. If the molecule has a branched carbon chain, the longest normal chain occurring in the molecule is chosen as the starting point for naming the molecule, the positions of the alkyl groups, which occur as branchings or as side-chains, being indicated by figures. Table 8 gives examples for the isomeric alkanols with 3 to 5 C-atoms.

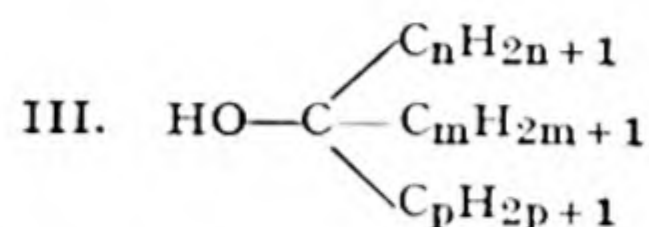
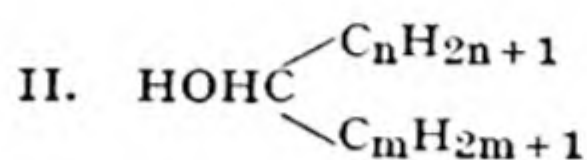
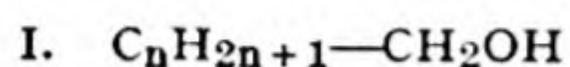
TABLE 8
ISOMERIC ALCOHOLS WITH 3 TO 5 C-ATOMS

Name	Formula	Boiling point	Melting point	Spec. grav. at 20° d_4^{20}
<i>Alkanols C₃H₇OH</i> Propanol-1 Propanol-2	CH ₃ CH ₂ CH ₂ OH CH ₃ CHOHCH ₃	97.2° 82.85°	—126.1° — 89.5°	0.8035 0.7851
<i>Alkanols C₄H₉OH</i> Butanol-1 Butanol-2 2-Methylpropanol-1 2-Methylpropanol-2	CH ₃ CH ₂ CH ₂ CH ₂ OH CH ₃ CH ₂ CHOHCH ₃ CH ₃ CHCH ₂ OH CH ₃ CH ₃ C(OH)CH ₃ CH ₃	117.75° 99.50° 108.1° 82.55°	— 89.9° — —108° + 25.55°	0.8097 0.8078 0.8026 0.7867
<i>Alkanols C₅H₁₁OH</i> Pentanol-1 Pentanol-2 Pentanol-3 2-Methylbutanol-1 3-Methylbutanol-1 2-Methylbutanol-2 3-Methylbutanol-2 2,2-Dimethylpropanol-1	CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ OH CH ₃ CH ₂ CH ₂ CHOHCH ₃ CH ₃ CH ₂ CHOHCH ₂ CH ₃ CH ₃ CH ₂ CHCH ₂ OH CH ₃ CH ₃ CHCH ₂ CH ₂ OH CH ₃ CH ₃ CH ₂ C(OH)CH ₃ CH ₃ CH ₃ CHCHOHCH ₃ CH ₃ CH ₃ CH ₃ CCH ₂ OH CH ₃	137.9° 119.8° 116.1° 128° 132° 102.3° 112.9° 113°	— 78.8° — — — — — 8.6° — + 48°	0.8148 0.8092 0.8203 0.816 0.8092 0.8088 0.819 d_4^{19} —

The alcohols are differentiated into *primary*, *secondary* and *tertiary* alcohols according to whether the hydroxyl-group is combined with a primary, secondary or tertiary carbon atom.

In general, derivatives of alkanes are called primary, secondary or tertiary if they can be considered as having been produced by substitution of hydrogen atoms attached to a primary, secondary or tertiary carbon atom (see 20).

Thus primary alcohols are represented by the general formula I; secondary by II and tertiary by III.



29. Physical properties of the alkanols. Some physical properties of a number of normal primary alcohols are given in Table 9. The difference in the boiling points between two successive members of the series amounts to 18–20° except for the first two members. If the boiling points of the normal alcohols are compared with those of the isomers with branched chains (Table 8), then it appears that here again the boiling point is lower as more branchings occur in the carbon chain.

TABLE 9
SOME PHYSICAL CONSTANTS OF ALKANOLS

Name	Formula	Spec. grav. d_4^0	M.p.	B.p.	Difference in b.p.	Molecular heat of combustion, liquid p const.
Methanol	CH_3OH	0.810	— 97.1°	64.65°		173.6
Ethanol	C_2H_5OH	0.806	—114.15°	78.32°	13.62°	326.7
Propanol-1	C_3H_7OH	0.819	—126.1°	97.2°	19.09°	482.1
Butanol-1	C_4H_9OH	0.824	— 79.9°	117.75°	20.34°	638.1
Pentanol-1	$C_5H_{11}OH$	0.829		137.9°	20.15°	794.3
Hexanol-1	$C_6H_{13}OH$	0.833		157.5°	17.5°	950.5
Heptanol-1	$C_7H_{15}OH$	0.838	— 36.5°	173°	17.6°	1107
Octanol-1	$C_8H_{17}OH$	0.843	— 16.7°	195.5°	22.5°	1263
Nonanol-1	$C_9H_{19}OH$	0.841	— 5°	213.5°	18.0°	1420
Decanol-1	$C_{10}H_{21}OH$	0.839	+ 7°	231°	19°	1577

The alcohols are colourless compounds. The alcohols C_1 to C_3 are mobile liquids miscible with water in all proportions. From C_4 onwards they have a limited miscibility with water. Alcohols with 12 and more carbon atoms are solid at ordinary temperatures and very slightly soluble in water.

30. Methanol (methyl alcohol). Free methyl alcohol occurs in the vegetable kingdom only here and there in traces (in some essential oils); on the other hand, compounds containing a methyl group in the form of an ester (77) or an ether (41) are very widely distributed throughout the vegetable kingdom.

Formerly methanol was obtained on a large scale exclusively by the "dry distillation" of wood. In this process besides gases there is produced an aqueous liquid and wood tar, while wood charcoal remains behind in the retorts. The aqueous liquid contains 1-3 % of methanol, and in addition various other substances of which acetic acid (about 10 %) and acetone (about 0.5 %) are the most important. The acetic acid is fixed by treatment with lime; the methyl alcohol is then separated and purified by fractional distillation. Crude methyl alcohol is also called "wood spirit".

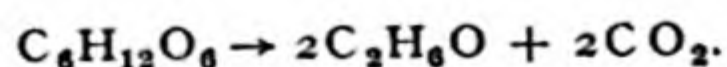
At present, methanol is prepared in a completely different manner, namely by catalytic reduction of carbon monoxide by hydrogen gas: $\text{CO} + 2\text{H}_2 \rightarrow \text{CH}_3\text{OH} + 21.8 \text{ kcal}$. This reaction takes place when a mixture of carbon monoxide and hydrogen is passed over certain catalysts at a pressure of 200 atm. and a temperature of about 400° (PATART; MITTASCH). The catalysts used for this purpose are obtained by reducing a mixture of zinc oxide and chromium oxide, to which other metal oxides are sometimes added, by means of hydrogen under pressure.

Higher alcohols (butanol) (34) are produced as by-products in this reaction along with methyl alcohol; the formation of these by-products can be facilitated by using certain catalysts. Thus the formation of methanol from CO and H_2 is a new example of specific catalysis in which the reduction of the carbon monoxide is directed into one particular direction (cf. 26).

Methanol is a clear, colourless liquid, miscible with water in all proportions; in this mixing development of heat and a contraction in volume occur. Methanol burns with a pale blue flame; the smell of methanol is very similar to that of ethyl alcohol. *Methanol is very poisonous.* In industry methanol is used, for example, in the preparation of formaldehyde, of several dyestuffs and for denaturing spirits.

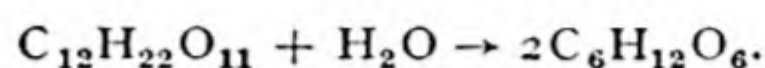
31. Ethanol occurs in the free state in nature only here and there in extremely small quantities, e.g. traces of ethanol have been detected in the soil, in natural waters and also in plants and in animal tissues.

Preparation. Ethyl alcohol, usually called alcohol for short, is usually obtained by fermentation of a sugar, glucose, $\text{C}_6\text{H}_{12}\text{O}_6$, which is split up into carbon dioxide and alcohol by the action of certain micro-organisms, yeast (163, 192):

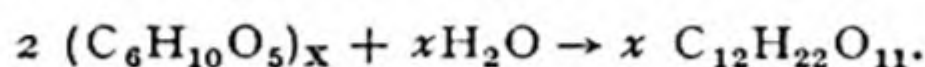


Glucose (which would be too expensive) is not used in the technical prepar-

ation of alcohol but material which is rich in starch, such as potatoes, corn, maize. Starch $(C_6H_{10}O_5)_x$ can be converted into maltose, $C_{12}H_{22}O_{11}$ (173, 182), by the action of certain *enzymes* (207). Glucose is produced from maltose by further hydrolytic fission, likewise under the influence of enzymes:



When potatoes are used as raw material they are heated with steam under pressure at about 130° , which bursts the cell walls and causes the starch grains to swell (183). The thin liquid mass so obtained, is then treated at about 60° with malt, *i.e.* germinated barley. The germinated barley contains enzymes, the amylases, together often called "*diastase*", which bring about the hydrolytic fission of starch into maltose:



When all this transformation, called *saccharification*, is at an end, yeast is added to the liquid; the yeast contains an enzyme *maltase*, which splits the maltose into glucose. The glucose so formed, is converted by the further action of the yeast into alcohol and carbonic acid; the fermentation is allowed to proceed at a temperature of $27-30^\circ$. The liquid is then subjected to distillation making use of a suitably constructed fractionating apparatus (column apparatus). In this way 90 % alcohol can be obtained directly although the concentration of alcohol in the fermented liquor is no higher than 18 %. The thin liquid mass remaining behind in the distillation kettle contains practically all the proteins which were present in the starting material and is used under the name of *swillings* as cattle food. The "raw spirit" is submitted to a fresh fractional distillation and 95.6 % alcohol is eventually obtained. The end-runnings from the distillation, the so called *fusel oil* consists of higher alcohols, chiefly of two pentanols (amyl alcohols) and contains also some propanol-1 and 2-methylpropanol-1. These higher alcohols, produced as by-products in alcoholic fermentation, are formed from proteins present in the starting material (see 195). At the present time ethanol is also produced on an industrial scale from ethene (see 85).

32. Since the system ethanol—water has a minimum boiling point at 78.15° at 95.57 % ethanol and 4.43 % water (6), 95.6 % alcohol cannot be concentrated further by distillation. In order to prepare anhydrous or *absolute alcohol*, 95.6 % alcohol is heated with quick-lime. The water present in the mixture then combines with the lime; on subsequent distillation pure ethyl alcohol passes over.

On the large scale, absolute alcohol is prepared by distilling alcohol containing water with the addition of benzene. The system benzene—alcohol—water shows a minimum boiling point at 64.9° ; the composition of this mixture is: 7.4 % water, 18.5 % alcohol and 74.1 % benzene. The system alcohol—benzene also shows a minimum boiling point at 68.2° ; the azeotropic mixture consists of 67.6 % benzene and 32.4 % alcohol. Hence, when alcohol containing water to which a sufficient quantity of benzene has been added is distilled, the ternary mixture boiling at 64.9° , mentioned above, will pass over first; this will go on until all the water has been removed from the liquid. Then the binary mixture boiling at 68.2° distils over; finally, absolute alcohol remains behind in the distillation apparatus and is run off. The benzene is used again.

Absolute alcohol is used for some industrial purposes, *e.g.* when admixed with petrol as a motor fuel.

Absolute alcohol is a colourless, mobile liquid with a characteristic odour, burning with a pale blue flame. It is hygroscopic and miscible with water in all proportions; on mixing, heat is developed and a contraction in volume occurs.

Ethyl alcohol and methyl alcohol are excellent solvents for a number of organic compounds and also for ammonia and hydrogen chloride; the chlorides and carbonates of the alkali metals are only slightly soluble in these alcohols.

If an aqueous solution of alcohol is saturated with potassium carbonate, immiscibility occurs and the liquid separates into two layers. The lower layer consists of a concentrated solution of potash containing only a little alcohol, the upper layer contains 91 % alcohol along with water and a little potash. This phenomenon of immiscibility also occurs with mixtures of water and some of the homologues of ethanol; use is made of this property for isolating such alcohols.

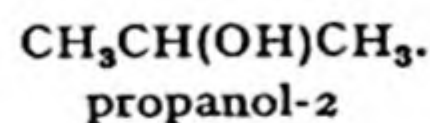
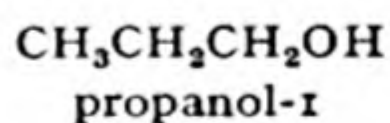
Ethanol is detected qualitatively by the iodoform reaction (see 107). Further, ethyl alcohol can be detected with certainty by treatment with *p*-nitrobenzoyl chloride (261) by which the ethyl ester of this acid melting at 57° is produced.

Alcoholic drinks were already known in ancient times and were prepared by primitive peoples from vegetable materials containing sugars or starch. One differentiates between *undistilled* alcoholic beverages such as wine (8–10 % alcohol), beer (3–4 % alcohol) and *distilled* alcoholic liquors, which are obtained from the former by distillation. To the second group belong *brandy* (40–50 % alcohol), *gin* (alcohol distilled over juniper berries), *cognac* (obtained from wine by distillation and containing more than 50 % alcohol).

Taken in small quantities, ethyl alcohol exerts a stimulating action which is soon followed however by a stupefying and soporific effect; in larger quantities alcohol acts as a poison; the ethyl alcohol is assimilated almost completely by the body but injurious effects are produced in the process, which may lead to degeneration of various organs in cases of chronic alcoholism.

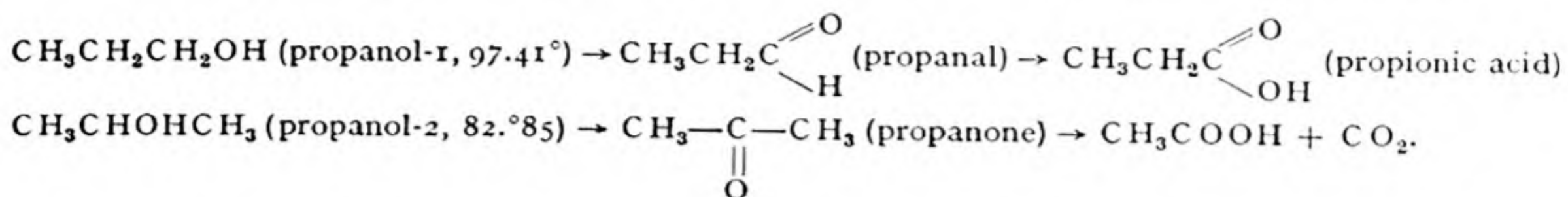
Ethanol is used for a number of industrial purposes, *e.g.* the preparation of lacquers and varnishes, in the manufacture of organic dyestuffs and pharmaceutical products.

33. Propanols (*Propyl alcohols*). There are two propanols; the one boils at 97.41° at 760 mm and has a spec. grav. of 0.8044 at 20°; the other has a boiling point of 82.85° and a spec. grav. of 0.7887 at 20°. According to the principles already put forward, only two isomers are possible, viz.:



It is possible to deduce which structure shall be ascribed to the alcohol boiling at 97.41° and which to the alcohol of b.p. 82.85°, by oxidation. By oxidation with potassium bichromate and sulphuric acid there is produced from the first alcohol a compound, *propanal*, having the composition $\text{C}_3\text{H}_6\text{O}$, from which propionic acid is produced on further oxidation with potassium permanganate. From the lower boiling alcohol oxidation with potassium bichromate and sulphuric acid likewise produces a compound of the com-

position C_3H_6O , propanone, but this is decomposed into acetic acid and carbon dioxide by further oxidation with potassium permanganate;



The formation of propionic acid from propanol-1 amounts to the replacement of two hydrogen atoms by one oxygen atom. It is clear that a compound of the structure of propionic acid can be produced from the primary alcohol (propanol-1), but not from the secondary alcohol (propanol-2).

This course of the oxidation is characteristic for all primary and secondary alcohols. A primary alcohol has the grouping $-CH_2OH$, which is converted by oxidation into the grouping $-C \begin{array}{l} \nearrow O \\ \searrow OH \end{array}$ characteristic of the carboxylic acids; a secondary alcohol has the grouping $>C \begin{array}{l} \nearrow H \\ \searrow OH \end{array}$, from which the group $>C=O$, characteristic of ketones, *i.e.* the general name for propanone and its homologues, is produced on oxidation.

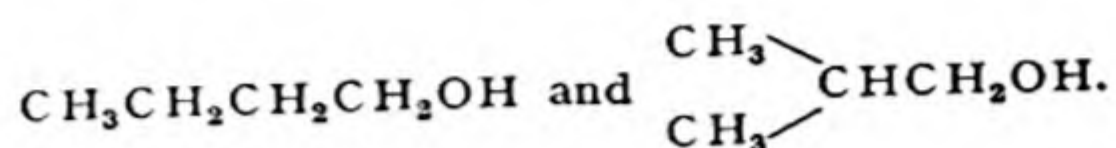
Thus on oxidation, primary alcohols give acids with the same number of carbon atoms; secondary alcohols give ketones with the same number of carbon atoms.

As follows from the example discussed above, the propanols are easily attacked by oxidising agents. This holds in general for all alcohols. While the saturated hydrocarbons, C_nH_{2n+2} , are difficult to oxidise, compounds, which may be thought of as being derived from these hydrocarbons by replacing a H-atom by the group $-OH$, are much more easily accessible for oxidation. At the same time there is one other point. Both in the conversion of propanol-1 into propionic acid and in the formation of acetone from propanol-2, oxidation takes place on the carbon atom to which oxygen is already attached. As a general rule it may be stated that: *When an organic compound is subjected to oxidation, the molecule is attacked at the place where oxygen is already present.*

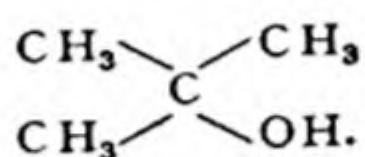
Propanol-1 occurs in fusel oil (31) and is obtained from it by fractional distillation; propanol-2 can be prepared by the catalytic reduction of propanone (65). Propanol-2 is prepared from propene (see 85) on an industrial scale. Both alcohols are poisonous; they are used as solvents.

34. Butanols. C_4H_9OH . There are four known alkanols C_4H_9OH (see table p. 58) *i.e.* as many as are possible from theory. Two of these, namely, those boiling at 117.75° and 108.15° at 760 mm., are oxidised to acids with the same number of carbon atoms.

Hence the following structural formulae come into consideration for these alcohols:



We shall see later that the normal structure must be ascribed to the alcohol with b.p. 117.75° , while the other structural formula belongs to the alcohol with b.p. 108.15° . A third butanol boiling at 99.5° can be converted by oxidation into a ketone with the same number of carbon atoms; hence this is a secondary alcohol having the structure $\text{CH}_3\text{CH}_2\text{CHOHCH}_3$. The fourth butanol is solid at ordinary temperature (m.p. $+25.45^\circ$) and boils at 82.55° . For this alcohol there remains the fourth structural formula, that of a tertiary alcohol (BUTLEROW):



When this alcohol is subjected to oxidation neither an acid nor a ketone with four carbon atoms is produced, but the molecule is immediately broken down to molecules with smaller numbers of carbon atoms. Since oxidation takes place at the carbon atom already carrying an oxygen atom, according to the structural formula given above one or more bonds between carbon atoms must be broken in the process with consequent break down of the carbon skeleton into smaller fragments. In general it holds that *a tertiary alcohol is split up by oxidation into compounds containing a smaller number of carbon atoms.*

Butanol-1 or normal primary butyl alcohol, is prepared technically by subjecting starch to a fermentation process under the influence of certain micro-organisms (*bacillus amylobacter*); acetone and ethanol are also produced in the process.

2-Methylpropanol-1 or primary isobutyl alcohol, is separated from fusel oil and is also obtained as a by-product in the methanol synthesis from carbon monoxide and hydrogen (by using cobalt catalysts) (30).

35. Pentanols (Amyl alcohols). Eight isomers are possible of the alcohols with 5 carbon atoms; all these are known (see table 8 on p. 58). Crude amyl alcohol from fusel oil consists of a mixture of 2-methylbutanol-1 (b.p. 128°) and 3-methylbutanol-1, (b.p. 132°), the latter predominating. These pentanols have a more powerful anaesthetic action and are more poisonous than ethanol. Butanols and pentanols are used as solvents especially in the manufacture of soluble lacquers.

Higher alcohols $\text{C}_n\text{H}_{2n+1}\text{OH}$. Some of these alcohols occur in nature in the form of derivatives. Thus esters of *n-hexanol-1*, *n-octanol-1* and *n-nonanol-1* are met with in essential oils.

Cetyl alcohol or *n-hexadecanol-1*, $\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{OH}$, occurs in the form of its palmitate ester in spermaceti. Esters of higher alcohols (with 24 to 36 carbon atoms) with fatty acids of 24 to 34 carbon atoms occur in different kinds of waxes, *e.g.* in bees, wax and in carnauba wax (a vegetable wax).

36. *Alkanolates* (*alcoholates* or *alkoxides*) are compounds produced from alcohols by replacement of the hydrogen atom of the hydroxyl-group by metals. The most important are *sodium methyrate* CH_3ONa and *ethylate* $\text{C}_2\text{H}_5\text{ONa}$, both white powders, easily soluble in the corresponding alcohols. These alcoholates are frequently used in organic syntheses; a solution of sodium methyrate in methanol is more stable than an ethyl alcoholic solution of the ethylate, which slowly becomes brown on account of oxidation (formation of aldehyde resin).

While the alcoholates of the alkali metals are produced directly by the action of the metal on the anhydrous alcohol, this reaction does not occur with other metals. Alcoholates of other metals are obtained by roundabout ways, *e.g.* by dissolving an alkali metal alcoholate in liquid ammonia and introducing a metal salt: $2\text{C}_2\text{H}_5\text{OK} + \text{Ba}(\text{NO}_3)_2 \rightarrow (\text{C}_2\text{H}_5\text{O})_2\text{Ba} + 2\text{KNO}_3$.

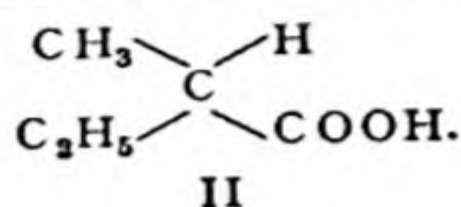
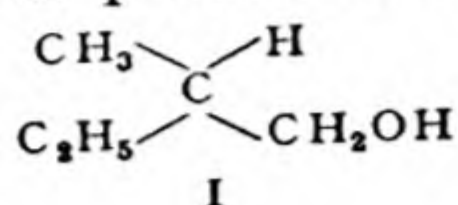
Relationship between optical activity and chemical structure; Stereoisomerism

37. Some substances are known, both inorganic and organic, which in the crystalline state cause a rotation of the plane of polarisation, *e.g.* crystals of quartz, potassium chlorate, benzil. These substances show no optical activity in the fused or dissolved state, so that in this group of compounds the optical activity is connected with the crystal structure.

A large number of compounds are known, which show optical activity in the fused state or in solution (13). In liquids the molecules are constantly in motion with regard to one another and there is no regular order as in a crystal. The optical activity of liquids cannot be ascribed therefore to a definite arrangement of the molecules, but must be connected with the internal structures of the molecule. This is apparent also from the fact that an optically active substance (turpentine oil) brings about a rotation of the plane of polarisation in vapour of normal density, as was proved by BIOT and later by GERNEZ. In this book, if optical activity is mentioned, it will refer to the optical activity of liquid or dissolved substances.

We shall illustrate the connection between optical activity and the structure of the molecule by the example of 2-methylbutanol-1. This alcohol as isolated from fusel oil is optically active and laevo-rotatory: $(\alpha)_D = -5.90^\circ$; the boiling point is 128° and the spec. grav. at 20° , 0.816. An isomer of this substance, having the same boiling point and the same specific gravity, but which is optically inactive, has been made synthetically. At the same time a third isomer has been obtained; again this has the same boiling point, and is optically active but rotates the plane of polarisation of polarised light towards the right. The same structural formula I, must be ascribed to each of these three isomers. This follows, for example, from the fact that

methylethylacetic acid, the structure of which has been proved by synthesis as II (see 124), is produced from each of these alcohols on oxidation:



Thus we have here three isomeric compounds which are identical in most chemical and physical properties, but which differ sharply from one another in one physical property, namely, in behaviour towards polarised light. The atoms and groups of atoms in the molecules of these three isomeric compounds are arranged in the same way, at least in the sense of the ideas so far developed. It is however possible to give an explanation of this peculiar kind of isomerism by an extension of the theory of structure.

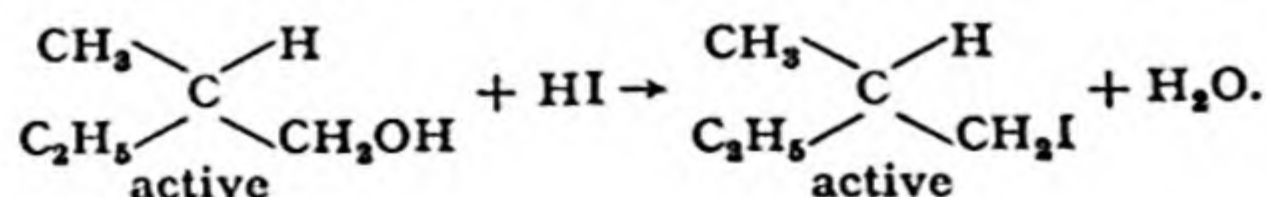
We will consider optically active forms only at first. Such isomers, one of which rotates the polarised light to the right and the other to the left, are called *optical antipodes*. It has been found that the numerical value of the rotatory power is the same for optical antipodes, only the sign is different (a rotation towards the right is called positive, and a rotation towards the left negative).

The first example of optical antipodes was discovered by L. PASTEUR during his investigations on the tartaric acids (138). In 1860 this investigator proposed the hypothesis that optically active bodies should have asymmetrically constructed molecules ("Dissymétrie moléculaire"). Such asymmetric molecules will be capable of existence in two forms, which will be mirror images of one another, and which are not therefore congruent; the dextro-rotatory isomer should consist of molecules of the one form and the laevo-rotatory of molecules of the other form.

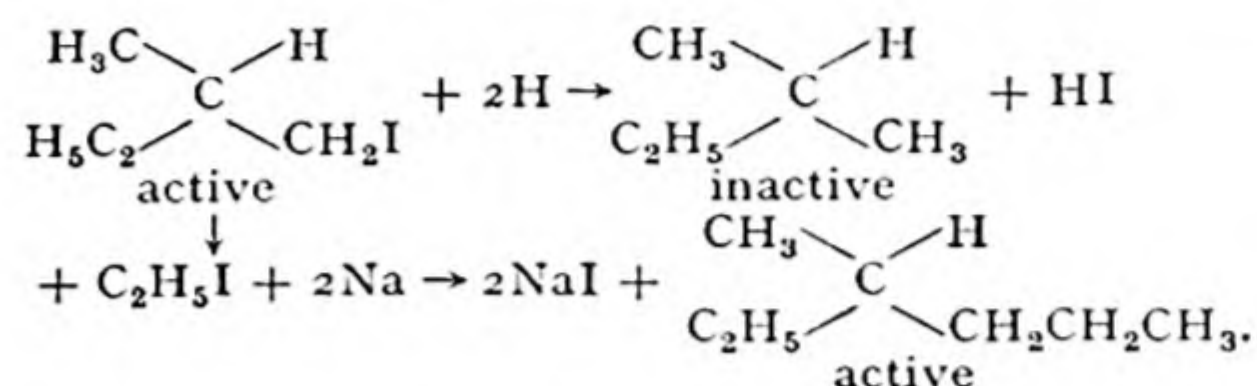
In 1874 J. H. VAN 'T HOFF and J. A. LE BEL independently of each other and in slightly different forms, extended the theory of structure so as to give a more accurate definition of PASTEUR's principle of molecular asymmetry.

VAN 'T HOFF noted that in all the optically active compounds of which the structure was then known, there occurred at least one carbon atom which was attached to four different groups. He called such a carbon atom an "asymmetric carbon atom".

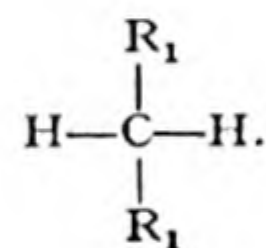
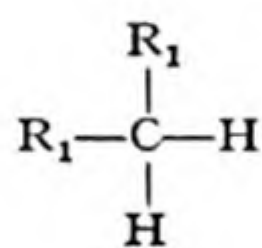
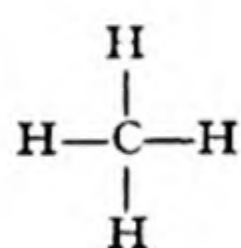
If such changes are brought about in the molecule of an optically active substance that there is no longer an asymmetric carbon atom present in the newly formed molecule, the optical activity disappears, as is shown by the following example. The laevo-rotatory pentanol was converted into a pentyl iodide, which was also optically active, by treatment with hydriodic acid:



By reduction with zinc and hydrochloric acid, this active pentyl iodide was converted into the corresponding hydrocarbon, 2-methylbutane, which was optically inactive. On the other hand, when the optically active pentyl iodide is treated with ethyl iodide and sodium, an optically active heptane (3-methylhexane) was produced:



Why is it now that molecules in which a carbon atom occurs combined with four different groups, must have an asymmetric structure? To explain this VAN 'T HOFF introduced a hypothesis regarding the directions of the bonding forces originating from the carbon atoms. He points out that the directions of these bonds in a molecule of methane cannot be situated in a flat plane because there would then be the possibility of drawing up two isomeric configurations for a di-substituted derivative of methane ($\text{CH}_2\text{R}_1\text{R}_2$), which should be paralleled with a difference in properties:



Phenomena which would indicate the presence of such isomers have never been found among di-substituted derivatives of methane, however. VAN 'T HOFF now assumes a *three-dimensional distribution* of the bonding forces of the carbon atom and in such a way that the bonding forces or valency bonds are directed towards the corners of a tetrahedron with the carbon atom situated at the centre.

In methane itself the arrangement of the four equivalent hydrogen atoms around the carbon atom will be such that the configuration of a regular tetrahedron is produced (Fig. 13). The same holds in general for a substance of type CX_4 , in which X represents a univalent atom or a univalent group. Both the distances between C and X and the angles between the four directions CX are mutually equivalent.

If however a hydrogen atom in CH_4 is replaced by the group R_1 (Fig. 14), the tetrahedral configuration which is produced, will have a lower symmetry than in the first case. The distance from R_1 to the C-atom will in general not be the same as the distance between a H-atom and the C-atom. Such a figure has a trigonal axis of symmetry (the line CR_1 in Fig. 14) and can

be covered by its mirror image. Hence a compound of type CH_3R_1 cannot occur in isomeric forms.

If now a second hydrogen atom is substituted by a group R_2 , further alterations will occur in the distances from the central carbon atom to the surrounding groups and in principle also in the angles between the directions of the bonds. However, the resultant configuration still has a plane of symmetry (which can be drawn through C, R_1 and R_2); this figure also is identical with its mirror image (Fig. 15).

Hence only one configuration can be drawn for the tetrahedral model of a compound $\text{CH}_2\text{R}_1\text{R}_2$, which is in agreement with the experience that compounds of this type do not exist in isomeric forms.

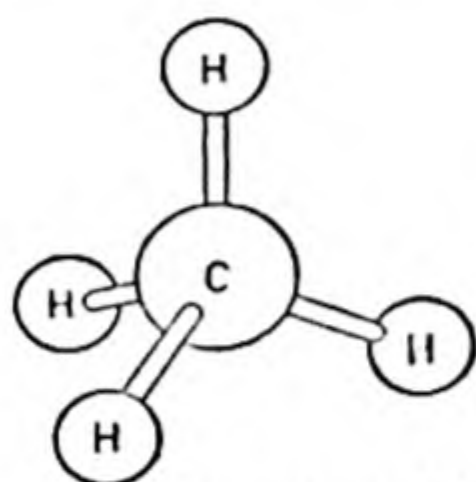


Fig. 13. Methane without substituents; arrangement for a regular tetrahedron

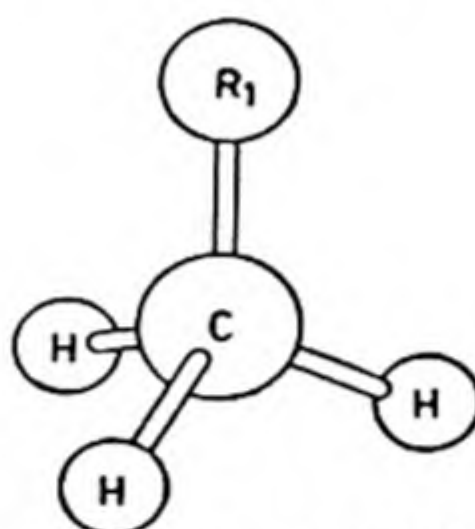


Fig. 14. Methane with one substituent; trigonal axis of symmetry. No isomeric forms possible

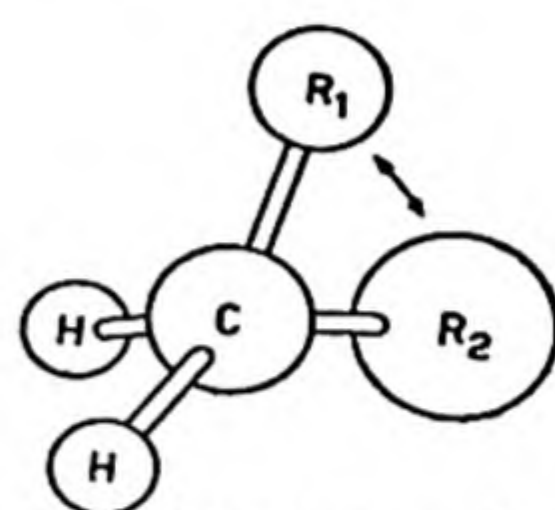


Fig. 15. Methane with two substituents; irregular tetrahedron. No isomeric forms possible

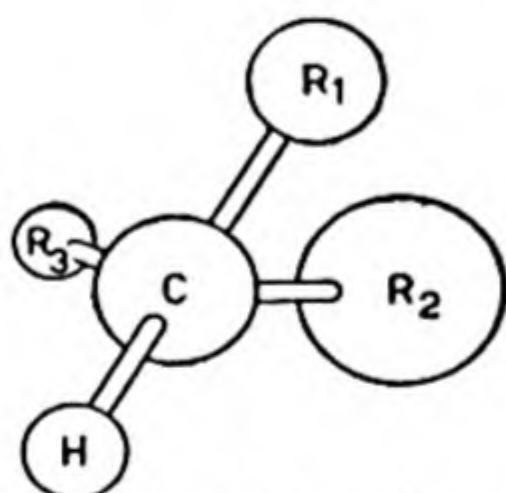


Fig. 16. Methane with three substituents; irregular tetrahedron. Isomeric forms possible

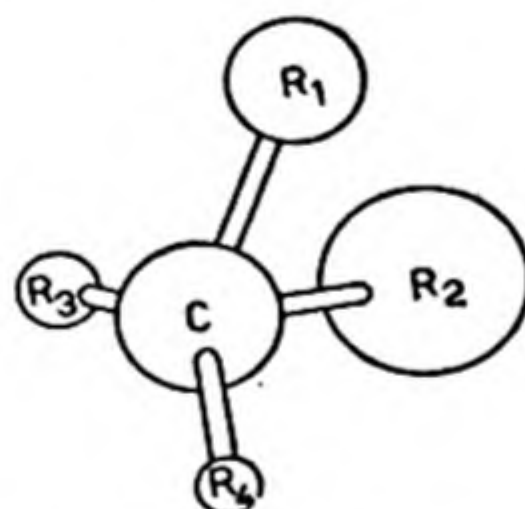


Fig. 17. Methane with four substituents; mirror images arrangement for irregular tetrahedra. Isomeric forms possible

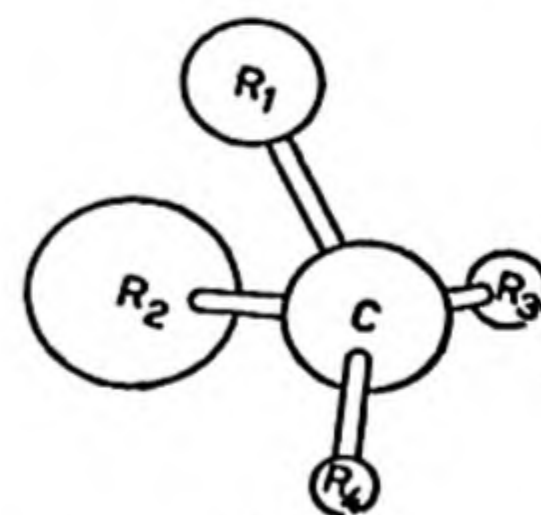


Fig. 18.

When a third hydrogen atom is replaced by a group R_3 , however, an irregular tetrahedral configuration (Fig. 16) is produced. In this case both the distances C—H , C—R_1 , C—R_2 and C—R_3 , and the angles between these bond directions are mutually different. This figure possesses no plane of symmetry nor even a centre of symmetry.

Thus for a molecule of the type $\text{CHR}_1\text{R}_2\text{R}_3$ or in general $\text{CR}_1\text{R}_2\text{R}_3\text{R}_4$, two mirror image configurations (Fig. 17 and 18) can be drawn, which cannot

be made to fit over each other. It is impossible to put both models into such a position that all the similarly named groups coincide.

A chemical compound, the molecule of which contains an asymmetric carbon atom in the sense of VAN 'T HOFF's hypothesis, will therefore be capable of existing in two isomeric forms agreeing with the two noncongruent mirror image forms of the molecule. The fundamental relationship between molecular asymmetry and rotation of the plane of polarisation can be derived from the electromagnetic theory of light. Taking this relationship as granted, it is then understandable that the one mirror image form rotates the plane of vibration of the polarised light to the right, the other mirror image form rotating it exactly the same amount to the left. Indeed, the nature of the groups of atoms on which the numerical value of the rotatory power depends, is the same in both kinds of molecule. The order of these groups in the two space models is different however; therefore, the action which the field of force of the molecule exerts on the beam of polarised light, is exactly opposite in direction for the two mirror image forms. Properties such as boiling point, solubility, vapour pressure, specific gravity, heat of combustion, are indicated by a figure only; in these cases there is no question of a direction (*scalar properties*). In all cases where these physical constants for optical antipodes have been accurately investigated exactly the same value has been found.

Optically inactive 2-methylbutanol-1 consists of a mixture of equal parts of dextro- and laevo-rotatory forms. Since these antipodes have the same boiling point, solubility, etc., a mixture of equal parts of the two will behave in most operations like a pure substance; indeed the usual methods of separation just depend on a difference in these properties. Later on we shall learn of methods by which a mixture of optical antipodes can be resolved into the optically active components (138). As regards chemical reactions optical antipodes behave exactly alike, except in the case where the reacting substance itself has an asymmetric structure.

From the above, the theory of VAN 'T HOFF-LE BEL gives a complete explanation of the isomerism phenomena observed with 2-methylbutanol-1 and very many other substances.

The essential of this theory is that a definite direction is allotted to the bonding forces of the carbon atoms, which in methane and its derivatives leads to a tetrahedral arrangement. Since the arrangement of the atoms in a space model of the molecule is being considered, one speaks of *stereochemical structure* or *stereostructure*. Isomers which are distinguished by a difference in the arrangement of the atoms in space, are called *stereoisomers*. Stereoisomerism does not arise exclusively with optically active substances; later on we shall learn about other kinds of stereoisomers (126, 140) and see again

how stereochemical theory can provide an explanation of the phenomena.

The general condition for the occurrence of optical antipodes is that the molecule shall contain neither a plane nor a centre of symmetry; only when these elements of symmetry are missing can the molecule occur in two noncongruent mirror images (PASTEUR's principle of molecular dissymmetry). The arrangement of four different groups round an asymmetric carbon atom (in the sense implied by VAN 'T HOFF and LE BEL) is one of the ways in which this condition can be fulfilled. In section 92 we shall be discussing compounds in which these elements of symmetry are still missing, so that they can occur in noncongruent mirror images, although their molecules contain no asymmetric carbon atom.

When the electronic formula of methane (22) is set out in a tetrahedral model, the nucleus of the carbon atom is placed at the centre of gravity of the tetrahedron and a pair of electrons which bring about combination with a proton, are found at each corner. The electronic formulae of other saturated aliphatic compounds are represented in the same way in three-dimensional models; the pairs of electrons are always arranged tetrahedrally around the nuclei of the C-atoms.

It is to be expected that optical activity may also occur in compounds in which an atom of another element, combined with four different groups, is present in place of an asymmetric carbon atom. We shall discuss optically active compounds in which the asymmetry of the molecule is caused by an "asymmetric nitrogen atom" or by "asymmetric atoms" of silicon, phosphorus (139), sulphur, tellurium (see 141).

The theory of VAN 'T HOFF and LE BEL on the tetrahedral structure of the alkanes and their derivatives has been confirmed by modern physical investigations on molecular structure. The distances between the atomic nuclei in a molecule can be derived from:

1. X-ray analysis of crystals,
2. measurements of the interference phenomena caused by electron diffraction with gaseous molecules of simple structure,
3. measurements of the infra-red absorption spectrum of substances with molecules containing a small number of atoms.

In this case use is made also of the RAMAN spectrum.

Not only can the distances of the atomic nuclei be derived from these measurements but also the size of the angles between the bonding forces (valency bonds); in this connection use is also made of measurements of the dipole moment. In calculating atomic distances and bond angles by these methods, the structure of the molecule derived from chemical reactions is taken into account; it is found that the results of physical measurements are in excellent agreement with the molecular models based on organic chemical structure theory. The physical measurements have taught us the dimensions of the molecule.

The atomic distances found by different methods are in good agreement.

TABLE 10
ATOMIC DISTANCES

Distance between atomic nuclei	Length in 10^{-8} cm. (Å)
C — C bond in diamond	1.54
C — C „ „ graphite	1.42
C — C „ „ alkanes	1.54
C = C „ „ alkenes	1.34
C ≡ C „ „ ethyne	1.20
C — H „ „ methane	1.09
C — H „ „ ethene	1.06
C — F „ „ fluoromethane	1.4
C — Cl „ „ chloromethane	1.7
C — Br „ „ bromomethane	1.9
C — I „ „ iodomethane	2.1
C = O „ „ urea	1.25
C = O „ „ carbon oxychloride	1.25

For the alkanes it has been found that the angles between the directions of the bonds differ but slightly from $109^{\circ} 28'$, the value which follows from the tetrahedral model for methane.

From measurements on electron diffraction, PAULING and his co-workers find $111^{\circ} 30'$ for the angle between the C—C bonds in propane and isobutane. Substitution of a halogen atom causes no significant alteration. In $\text{CH}_3\text{CH}_2\text{Cl}$ the angle between the C—Cl bond and the C—C bond is $111^{\circ} 30'$; in CH_2Cl_2 the angle between the C—Cl bonds is 112° .

From the X-ray analysis of crystalline *n*-nonaeicosane, $\text{C}_{29}\text{H}_{60}$, it follows that the carbon atoms lie in a flat plane in the form of a zig-zag chain. The angles between the C—C bonds is 109° ; the distance between two successive C-atoms is 1.54 Å, the distance between the 1st, 3rd, 5th, etc., C-atom amounts to 2.54 Å (A. MULLER).

In the examination of crystalline higher fatty acids such as lauric acid and stearic acid (74) long zig-zag chains have again been found with C—C distances of 1.54 Å and angles of 109° .

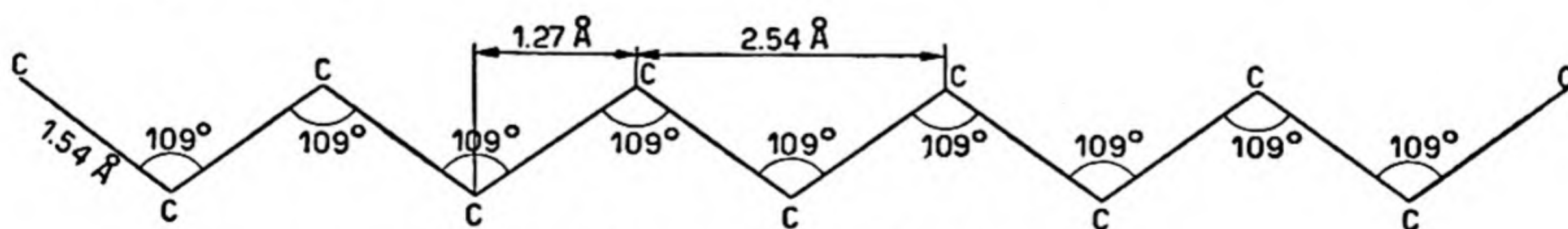
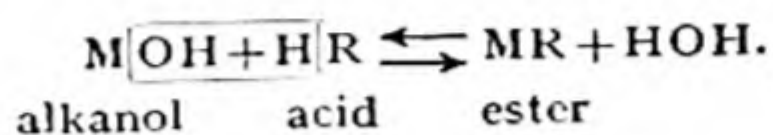


Fig. 19. Zig-zag chains of carbon atoms

From Fig. 19, it appears that the length of the carbon chain increases by 1.27 Å for each CH_2 -group (compare 74 and 79).

(ii) ESTERS OF INORGANIC ACIDS; ETHERS

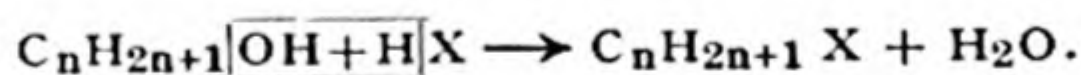
38. Many compounds are known in inorganic chemistry which contain a hydroxyl group, *e.g.* the bases, which are able to form salts with acids with the elimination of water. A similar reaction is known with the organic hydroxyl-compounds, the alcohols, which also react with acids with the elimination of water:



The compounds which are produced in this way are called *esters*. There is however a great difference in the reaction velocity between the formation of a salt from an acid and a base, and the formation of an ester from an acid and an alcohol. A solution of an inorganic base in water contains hydroxyl ions; the reaction with the similarly ionised acid takes place between the ions. Such ionic reactions take place very rapidly. An aqueous solution of an alcohol does not react alkaline and it does not conduct an electric current; thus alcohols are not ionised in solution and are completely different in this respect from inorganic bases. The formation of an ester from an alcohol and an acid takes place therefore between the undissociated molecules. In general, such reactions take place much more slowly than reactions between ions.

There exists an analogy between bases and alcohols in one other respect. Many bases can lose water and are then converted into anhydrides or oxides. Thus by splitting off a molecule of water from two molecules of alkanol compounds of the type $\text{C}_n\text{H}_{2n+1}\text{—O—C}_n\text{H}_{2n+1}$ are produced; these substances are called *ethers*.

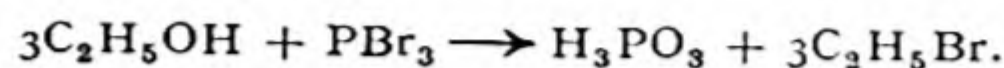
39. *Halogenoalkanes (Alkyl halides)*. These compounds may be considered as esters of alkanols and hydrogen halides, as appears from their method of formation:



The alcohol is saturated with dry hydrogen halide and the mixture warmed. The alkanol may also be heated with a concentrated solution of the acid in water with the addition of calcium chloride if the chloro-compound is being prepared; the halogeno-alkanes then distil over.

The *action of phosphorus halides on alcohols* (see 28) is frequently employed for the preparation of halogenoalkanes. Because in many cases this reaction takes place with considerable violence, for preparing *alkyl bromides or iodides* it is usual to start from phosphorus and bromine (or iodine) separately rather than from PBr_3 or PI_3 . As an example, red phosphorus is added to

ethanol in which it does not dissolve, and then bromine is added slowly drop by drop with cooling; the bromine forms PBr_3 with the phosphorus, which then reacts with the alcohol:



The ethyl bromide (b.p. 38.4°) is then distilled off.

The halogenoalkanes are only very slightly soluble in water but readily soluble in many organic liquids; the lower members have a pleasant ethereal smell.

Table II below gives some of the *physical properties of the normal halogenoalkanes*.

TABLE II
SOME PHYSICAL CONSTANTS OF HALOGENO-ALKANES

Alkyl group	Fluoride	Chloride			Bromide			Iodide		
	B.p.	B.p.	M.p.	Spec. grav. 0°	B.p.	M.p.	Spec. grav. 0°	B.p.	M.p.	Spec. grav. 0°
Methyl CH_3	-78.4°	-24.1°	-97.7°	0.952	3.4°	-93.7°	1.7	42.3°	-66.1°	2.335
Ethyl C_2H_5	-32°	12.3°	-138.7°	0.921	38.4°	-119.0°	1.501	72.3°	-110.9°	1.984
n-Propyl C_3H_7	-3°	46.4°	-122.8°	0.914	70.8°	-109.8°	1.386	102.4°	-98.7°	1.784
n-Butyl C_4H_9	32.5°	78.5°	-123.1°	0.905	101.6°	-112.4°	1.303	130.4°	-103°	1.648
n-Pentyl C_5H_{11}	62.8°	105.7°		0.897	127.9°		1.243	153.3°		1.538

Chemical properties. The halogenoalkanes show a big difference from the halogeno-compounds of the metals in their action on silver nitrate. In aqueous alcoholic solution the latter give immediately a quantitative precipitate of silver halide. On the other hand, the silver halide is precipitated by silver nitrate only very slowly from a solution of the alkyl halides, the alkyl iodides reacting considerably more rapidly than the alkyl chlorides. This indicates also that a solution of an alkyl halide is not ionised or only to a very small extent.

Methyl and ethyl chlorides burn with a green-mantled flame by which these substances can be recognised; the other lower alkyl halides, such as ethyl bromide and iodide, are difficult to burn.

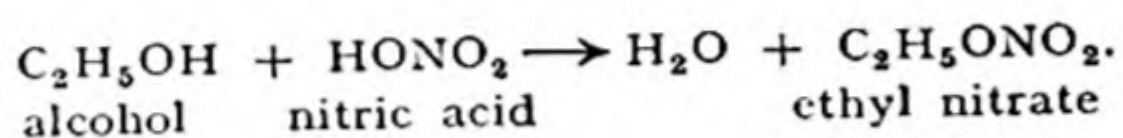
The halogeno-compounds can be converted one into the other. Thus alkyl iodides, for example, can be obtained by heating the chlorides with KI , CaI_2 , etc. These reactions, however, are frequently incomplete. The alkyl iodides especially are frequently used to introduce alkyl groups into organic compounds.

The halogen atom can be replaced by hydrogen with the regeneration of the corresponding hydrocarbons, C_nH_{2n+2} , by reducing agents such as zinc and hydrochloric acid, sodium amalgam and water, or by heating with hydriodic acid and red phosphorus.

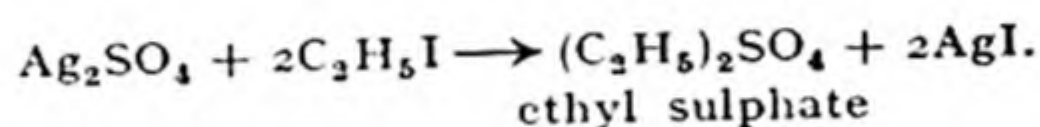
Alkyl fluorides are produced by the action of anhydrous hydrogen fluoride on alcohols and can be prepared by heating alkyl iodides with mercurous fluoride (SWARTS). The primary alkyl fluorides do not react or they react only very slowly with alcoholic alkali.

40. *Esters of other mineral acids* can be prepared by various methods:

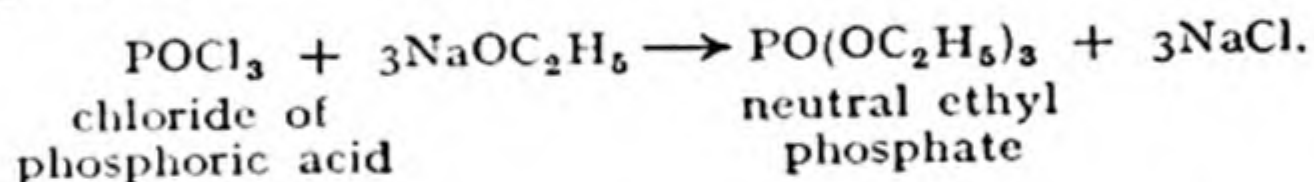
- a) Alkyl nitrates are produced by the action of nitric acid on the absolute alcohol:



- b) Alkyl sulphates are produced by the action of an alkyl halide on silver sulphate:



- c) Alkyl phosphates are produced, for example, by the action of the chlorides of the phosphoric acids on alcohols or alcoholates:

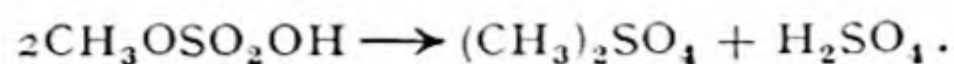


The *alkyl esters of sulphuric acid* are frequently used for chemical syntheses. The acid esters $C_nH_{2n+1}OSO_2OH$, which are also called alkylsulphuric acids, are produced by the action of concentrated sulphuric acid on alcohols, in which reaction a state of equilibrium is attained. In order to separate these acid esters from the remaining free sulphuric acid, use is made of the barium or calcium salts, which are readily soluble and therefore easy to separate from the insoluble barium sulphate after the reaction product from the alcohol and sulphuric acid has been neutralised with barium carbonate.

Ethylsulphuric acid, which can be obtained in a free state from the barium salt by adding the calculated quantity of sulphuric acid, is an oily liquid, miscible with water in all proportions and having the characteristics of a strong acid. This substance is split up into alcohol and sulphuric acid in dilute aqueous solution, slowly at ordinary temperatures and rapidly at higher temperatures. The salts of the alkylsulphuric acids crystallise well.

The neutral esters of sulphuric acid, e.g. dimethyl sulphate $(CH_3)_2SO_4$ and diethyl sulphate $(C_2H_5)_2SO_4$ are frequently used for introducing methyl groups or ethyl groups. They are oily liquids, immiscible with water.

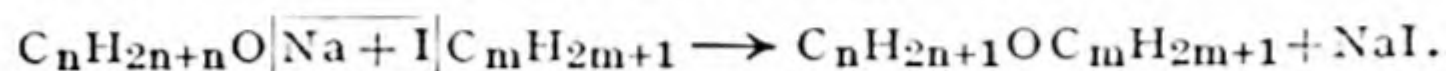
Dimethyl sulphate (b.p. 188°) is prepared by distilling methylsulphuric acid in a vacuum:



Dimethyl sulphate is very poisonous; it causes burns on the skin and attacks the respiratory organs.

ETHERS

4I. These compounds, which are isomeric with the alkanols, are formed by the action of alkanolates on halogenoalkanes (WILLIAMSON synthesis):

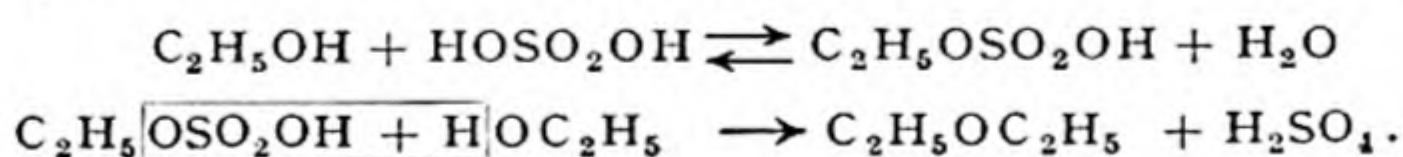


The structure follows from this synthesis and it also follows that the metal atom in the alkanolates occupies the same position as the hydrogen atom in the hydroxyl group. If the sodium atom in sodium methylate were attached to carbon, thus NaCH_2OH , propanol would be produced by the action of ethyl iodide: $\text{C}_2\text{H}_5[\text{I} + \text{Na}]\text{CH}_2\text{OH}$, which is not in agreement with experiment; the compound produced, *methyl ethyl ether* or *methoxyethane*, shows none of the properties of an alcohol.

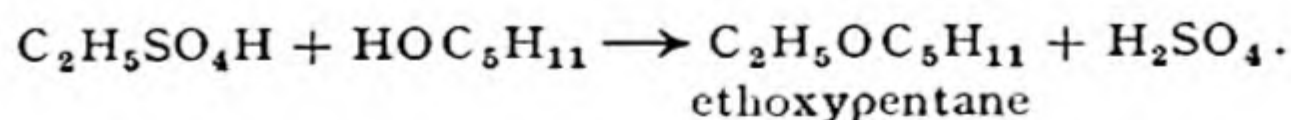
Nomenclature. The ethers are considered as alkanes substituted by alkoxy-groups: *e.g.* $\text{CH}_3\text{OC}_2\text{H}_5$, methoxyethane; CH_3OCH_3 , methoxymethane; $\text{C}_2\text{H}_5\text{OC}_5\text{H}_{11}$, ethoxypentane. Ethers with two similar alkyl groups are usually named after the alkyl groups, like dimethyl ether, etc. Ethers with two dissimilar alkyl groups, $\text{C}_n\text{H}_{2n+1}\text{OC}_m\text{H}_{2m+1}$, are called *mixed ethers*.

Diethyl ether is prepared technically and also in the laboratory from alcohol and sulphuric acid. On warming a mixture of these two substances in certain proportions to about 140°, ether is formed and distils from the mixture. Alcohol is then allowed to run in slowly and the formation of ether continues.

To explain this method of formation it is assumed (WILLIAMSON) that *ethylsulphuric acid* is first formed, which then reacts with a second molecule of alcohol to produce ether and regenerate sulphuric acid:



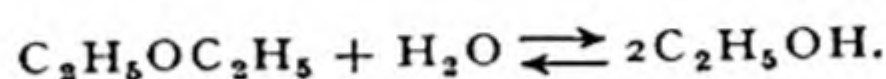
If another alcohol instead of ethanol is added in the second stage of the reaction, *i.e.* shortly before the distillation of ether begins, a mixed ether is formed:



This experiment supports the opinion that the reaction actually takes place in two stages.

Although the sulphuric acid is regenerated in the preparation of ether by this method, it is not possible to convert unlimited amounts of alcohol into ether with a limited amount of sulphuric acid. The water formed in the reaction partly distils over with the ether and part remains behind in the reaction vessel where it is held fast by sulphuric acid; when the water content of the mixture in the reaction vessel rises above a certain limit, the formation of ethylsulphuric acid stops and the formation of ether is prevented. Simultaneously side-reaction occur; the sulphuric acid acts as an oxidising agent and sulphur dioxide is produced.

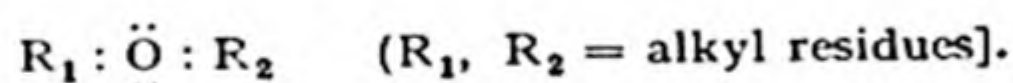
The formation of ether from alcohol is a reversible process. By heating diethyl ether with an excess of water and a little sulphuric acid it takes up a molecule of water and is split up into ethanol:



This reaction is facilitated catalytically by certain inorganic salts like copper sulphate and ferric sulphate, so that ether is formed by heating alcohol with one of these substances to 160–200° (VAN ALPHEN). According to a method discovered by SENDERENS, ethers can be prepared by passing alcohol vapour over aluminium oxide or aluminium sulphate at 240–260°. This method is suitable for the preparation of dimethyl ether; mixed ethers can also be obtained in this way.

The action of sodium alcoholate on a primary alkyl halide in many cases gives good yields of both simple and mixed ethers.

The electronic formula of an ether is represented as follows:

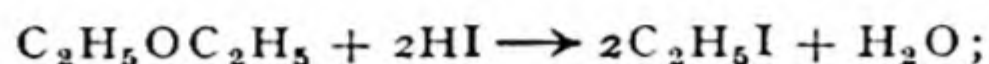


The oxygen atom in an ether molecule has two *lone pairs of electrons*.

Diethyl ether is a colourless, very mobile liquid; boiling point 34.6°, melting point –116.3°, spec. grav. 0.7199 (d_{15}^{15}). As a consequence of the low boiling point, ether is very volatile; since the vapour is extremely inflammable (with a luminous flame) and can give an explosive mixture with air, *great care* must be taken with this substance. The ethers have a characteristic “ethereal” odour. When the vapour of diethyl ether is breathed continuously unconsciousness is produced, hence the use of ether for anaesthesia. Ether is miscible with alcohol and is slightly soluble in water, at 20° 100 grams of water dissolve 7.5 grams of ether, while 100 grams of ether dissolve 2.7 grams of water at the same temperature.

In the laboratory, ether is an indispensable liquid for dissolving and re-crystallising numerous compounds or for extracting them from solution in water. Diethyl ether is used also in industry as a solvent and as an extraction medium. Unlike the alcohols, the ethers are inert towards sodium and

phosphorus pentachloride. Alkyl halides and water are produced by heating ethers with anhydrous hydrogen halides. Dry hydrogen iodide reacts with ethers already at ordinary temperatures according to the equation:



ethers are not attacked by alkalis.

In time, diethyl ether is oxidised to a small extent by the oxygen in the air at ordinary temperatures with the formation of explosive compounds having the properties of peroxides.

Dimethyl ether and dry hydrogen chloride combine at low temperatures to an addition-product of the composition $(\text{CH}_3)_2\text{O} \cdot \text{HCl}$, which breaks down again into its components above 0° , however.

Association. When the boiling points of the ethers are compared with those of the normal primary alcohols with the same number of carbon atoms (Table 12), it is apparent that the boiling point of an alcohol lies much higher than that of the ether, which is isomeric with it.

TABLE 12

BOILING POINTS OF ETHERS AND *n*-ALCOHOLS (SAME NUMBER OF C-ATOMS)

Ether		B.p.	Alcohol	B.p.
Dimethyl ether	$\text{C}_2\text{H}_6\text{O}$	-23.6°	ethanol	78.3°
Diethyl ether	$\text{C}_4\text{H}_{10}\text{O}$	34.6°	butanol-1	117.7°
Di- <i>n</i> -propyl ether	$\text{C}_6\text{H}_{14}\text{O}$	90.7°	hexanol-1	155.4°
Di- <i>n</i> -butyl ether	$\text{C}_8\text{H}_{18}\text{O}$	141°	octanol-1	195.5°

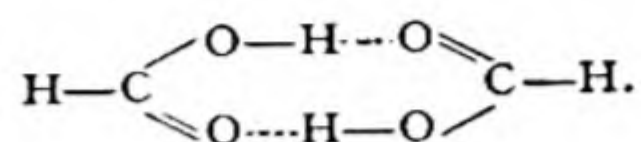
Also the *n*-alkyl chlorides (Table 11, p. 73) boil much lower than the corresponding alcohols. On the basis of observations on the alteration of the surface tension with the temperature or of measurements of the viscosity, it is assumed that in liquid alcohols the molecules are partly combined together to form aggregates, according to a statistical distribution between single molecules and aggregates of two, three or more molecules. This phenomenon called *association*, occurs in compounds containing hydroxyl groups.

Associated liquids show a deviation from TROUTON'S law. According to this law there exists an empirical relationship $\frac{\lambda}{T} \propto 21$ between the molecular heat of vapourisation (*i.e.* the latent heat of evaporation calculated per grammolecule) and the absolute boiling temperature *T*. This ratio of TROUTON amounts to 20–22 for a number of non-associated liquids, but is about 26 for water and alcohols.

The lower members of the series of alkane-carboxylic acids (67), *e.g.* formic acid and acetic acid, are strongly associated. This association differs from that of the alcohols in so far that in these acids aggregates of two molecules are formed. The vapour density of acetic acid at the temperature of the boiling point is twice as large as is required by the formula $\text{C}_2\text{H}_4\text{O}_2$; only at a temperature of about 250° is the normal vapour density observed. A large proportion of the acetic acid is still present in the form of double molecules also in a solution in a hydrocarbon, *e.g.* benzene, as is evident

from cryoscopic determinations. The esters of these carboxylic acids (77), however, are not, or only very slightly, associated; it appears from this that the phenomenon of association is connected with the presence of hydroxyl groups.

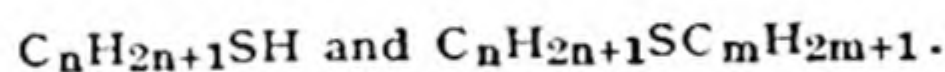
For the carboxylic acids it is assumed that the hydrogen atom of the hydroxyl group forms an electrostatic bond with the doubly bound oxygen atom of the COOH-group (*hydrogen bridge*), so that the dimer of formic acid is represented as follows:



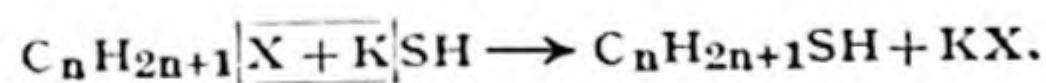
(iii) ALKYL ATTACHED TO SULPHUR

42. Elements in the same column of the periodic table show great similarity as is apparent from the study of inorganic chemistry. The mutual similarity and the graduated differences are very clearly apparent also in organic derivatives of these elements. The comparison of oxygen compounds with sulphur compounds of similar structure may well serve as a demonstration of this.

The alcohols and the ethers may be considered as having been derived from water by replacing one or both hydrogen atoms by alkyl. The corresponding sulphur compounds may be derived in the same way from hydrogen sulphide; thus they are represented by:



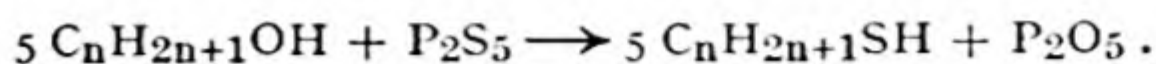
The former bear the name of *thiols*, the latter that of *thioethers*. The similarity of these compounds to the alcohols and ethers is apparent from their method of formation; if KSH instead of KOH is allowed to react with an alkyl halide, a thiol is formed:



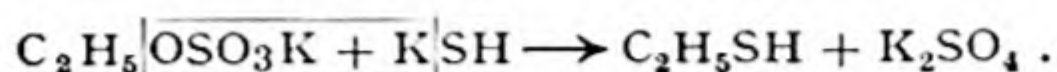
Like the alkanols the thiols have a hydrogen atom in their molecule which is replaceable by metals. It is obvious that this is the hydrogen atom attached to the sulphur. As in the method of formation of ethers from alkyl halides and alcoholates, thioethers are produced by the interaction of alkyl halides and the metal derivatives of thiols.

Comparing the alkanols with water, a neutral compound, and the thiols with hydrogen sulphide, a weak acid, the alcohols are neutral compounds while the thiols have an acid character. The alkanols do not give alkanolates with heavy metal bases whereas the thiols form thiolates. An alkanol, which is sparingly soluble in water, *e.g.* pentanol does not dissolve in dilute alkali. Thiols, which are insoluble in water, dissolve readily in alkali with the formation of thiolates.

43. Thiols or mercaptans. These compounds can be obtained by the action of P_2S_5 on alcohols:



or by distillation of a solution of potassium alkylsulphate with potassium hydrogen sulphide:

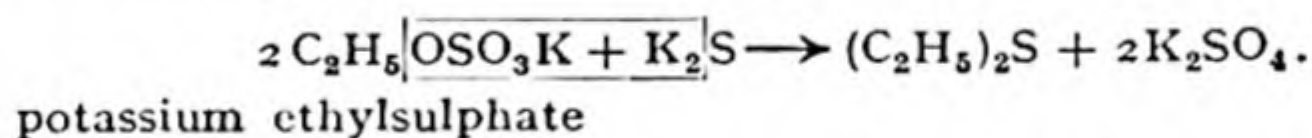


or by leading hydrogen sulphide charged with alcohol vapour over thorium oxide, ThO_2 , at $300-350^\circ$.

They are liquids, almost insoluble in water, with considerably lower boiling points than the corresponding alkanols; *methanethiol*, for example, boils at 6° , methanol at 66° . The lower boiling points of the thiols indicate that these compounds are not associated in the liquid state (cf. 41). The thiols are characterised by an extremely unpleasant smell; small traces which cannot be detected chemically are still recognisable by this means.

Many metal derivatives of thiols (*thiolates* or *mercaptides*) are known, some of which are well crystallised, e.g., the thiolates of mercury, which are produced by the action of thiol on mercuric oxide. The thiol is liberated again from the thiolate by mineral acids. The name mercaptan is derived from "corpus mercurio aptum", which refers to the formation of the crystalline mercury salts of the thiols.

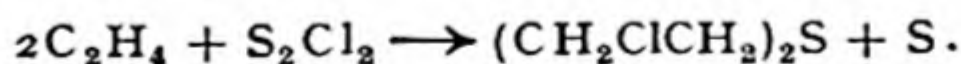
44. Thioethers. These compounds can be obtained by treating salts of alkylsulphuric acids with potassium sulphide, as well as by the method given in 42:



When thiols are passed in the vapour phase over cadmium sulphide heated to 300° , thioethers are produced along with hydrogen sulphide (SENDERENS). They are inert compounds, which when not quite pure give off an offensive odour. This may be removed by heating with copper powder.

The thioethers are liquids; they do not dissolve in water. They give double compounds e.g. $(C_2H_5)_2SHgCl_2$, with some metallic salts.

2,2-Dichlorodiethyl sulphide, used in the 1914-1918 war under the name of *mustard gas*, is produced by the interaction of ethene and sulphur chloride:



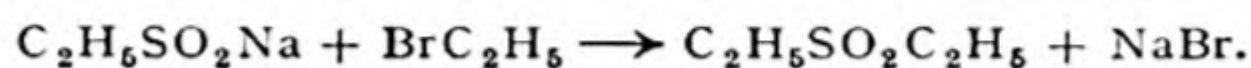
The vapours of this liquid boiling at 217° , which have a faint characteristic odour, have a destructive effect on the respiratory organs. The liquid itself causes serious burns on the skin, while the substance has a high penetrating power for animal tissues and splits off hydrochloric acid in these tissues. Since the isomeric 1,1-dichlorodiethyl sulphide, $(CH_3CHCl)_2S$, does not possess this property, it is non-injurious.

The thioethers have the remarkable property of combining with a molecule of alkyl iodide to give compounds easily soluble in water and having the properties of salts,

Since sulphur is attached directly to carbon in the thiols, it must be assumed that this is the case for the sulphonic acids also, which is confirmed by the fact that they can be reconverted into thiols by reduction. Hence the structure of *ethane sulphonic acid* is $\text{CH}_3\text{CH}_2\text{SO}_3\text{H}$.

The alkanesulphonic acids are strongly acid, very hygroscopic, crystalline compounds, which are very easily soluble in water.

In the compounds $\text{C}_n\text{H}_{2n+1}\text{SO}_2\text{Cl}$, called *alkanesulphonyl chlorides*, the Cl-atom is replaced by hydrogen by treatment with hydrogen in a nascent state; the compounds so obtained, $\text{C}_n\text{H}_{2n+1}\text{SO}_2\text{H}$, are called *alkanesulphinic acids*. When an alkyl halide is allowed to react on the sodium salt of a sulphinic acid, a sulphone (44) is produced:



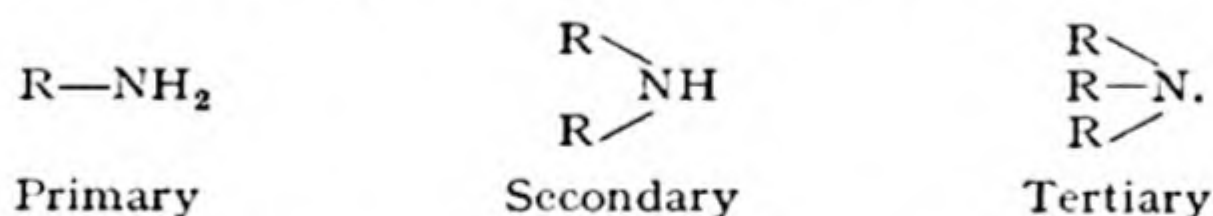
The structure of these compounds follows from this reaction.

(iv) ALKYL ATTACHED TO NITROGEN

(a) *Amines*

46. By *amines* is understood, in general, compounds which may be regarded as being derived from ammonia by replacing one or more of the hydrogen atoms by hydrocarbon residues. In this chapter we shall discuss the *alkylamines*, which were discovered by WURTZ in 1848 (155).

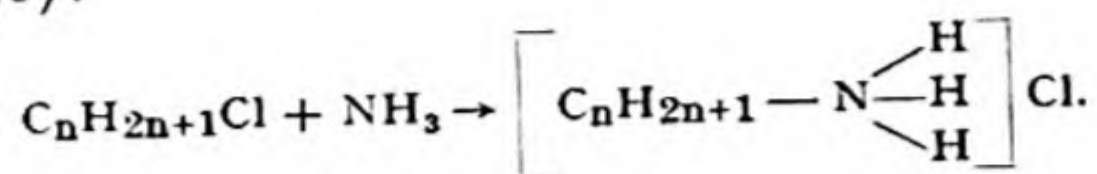
Nomenclature and isomerism. Amines with one nitrogen atom are considered as derivatives of ammonia and not as alkanes in which hydrogen is replaced by the group NH_2 . They are denoted by the suffix *ine*, which is distinctive for all basic substances containing nitrogen. According to whether one, two or three of the hydrogen atoms in ammonia are replaced by alkyl, the amines are designated *primary*, *secondary* or *tertiary*:



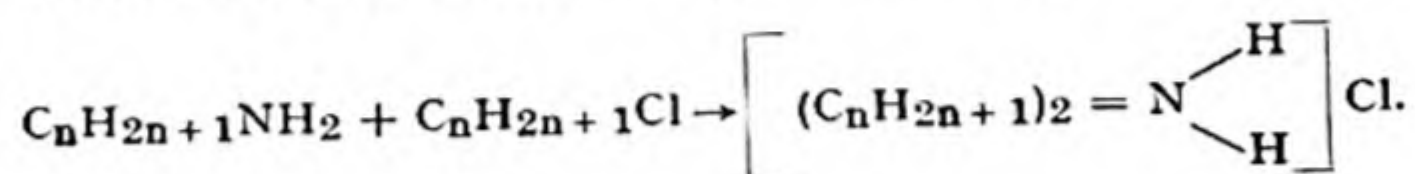
In the above formulae R is an alkyl residue; in secondary and tertiary amines the alkyl residues may be the same or different. The compounds NR_4OH , analogous to NH_4OH , *ammonium hydroxide*, bear the name of *quaternary ammonium bases*, the salts $(\text{NR}_4)\text{X}$, in which X is a monovalent anion, are called *quaternary ammonium salts*.

Isomerism in the amines may depend on branching of the carbon chain, on the primary, secondary or tertiary configuration of the nitrogen atom and on both these causes acting together. A compound $\text{C}_3\text{H}_9\text{N}$, for example, may be primary: propylamine $\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$ or isopropylamine $(\text{CH}_3)_2\text{CHNH}_2$, secondary: methylethylamine $\begin{array}{c} \text{CH}_3 \diagdown \\ \text{NH} \\ \text{C}_2\text{H}_5 \diagup \end{array}$, or tertiary: trimethylamine $\begin{array}{c} \text{CH}_3 \diagdown \\ \text{CH}_3-\text{N} \cdot \\ \text{CH}_3 \diagup \end{array}$.

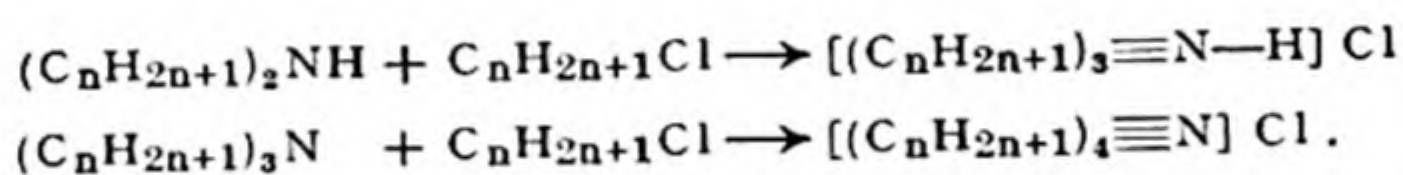
47. *Methods of formation.* When ammonia is heated with an alkyl halide in alcoholic or aqueous solution, the following reaction takes place (A. W. VON HOFMANN 1850):



The alkyl chloride, for instance, adds on to the ammonia with the production of the hydrochloride of a primary amine, in the same way as ammonium chloride is formed from NH_3 and HCl . The excess of ammonia present partially liberates the primary amine from the hydrochloride, $\text{C}_n\text{H}_{2n+1}\text{NH}_2 \cdot \text{HCl}$, and this then reacts in the same way with alkyl chloride:



The secondary amine also is partially liberated from the resultant hydrochloride and reacts further with the formation of a tertiary amine; finally, the tertiary amine adds on alkyl chloride and gives a quaternary ammonium salt:



In general the process proceeds in these four stages for any ratio of alkyl halide and ammonia. Hence the result is that primary, secondary and tertiary amine and quaternary ammonium salt are produced together. Sometimes it is possible to adjust the ratio of ammonia to alkyl halide, the duration of the reaction, etc., so that a particular amine is produced as the main product. Also the nature of the alkyl group has a great effect on the composition of the reaction product.

Salts of primary, secondary and tertiary amines are decomposed by alkali; quaternary ammonium salts are not. Therefore when a mixture of amine salts and a quaternary ammonium salt is made alkaline and distilled in steam, the primary, secondary and tertiary amines distil over and the quaternary compound remains behind.

Various methods exist for obtaining primary amines uncontaminated with secondary and tertiary amines; see 78. Pure dimethylamine can be obtained from *p*-nitrosodimethylaniline (237).

Basic character of the alkylamines. The most characteristic property of the amines is that they can combine additively with acids to form salts like ammonia. The methyl- and ethyl-amines are very readily soluble in water. At the same molar concentration the solutions show a higher conductivity for an electric current than solutions of ammonia; hence the amines are more

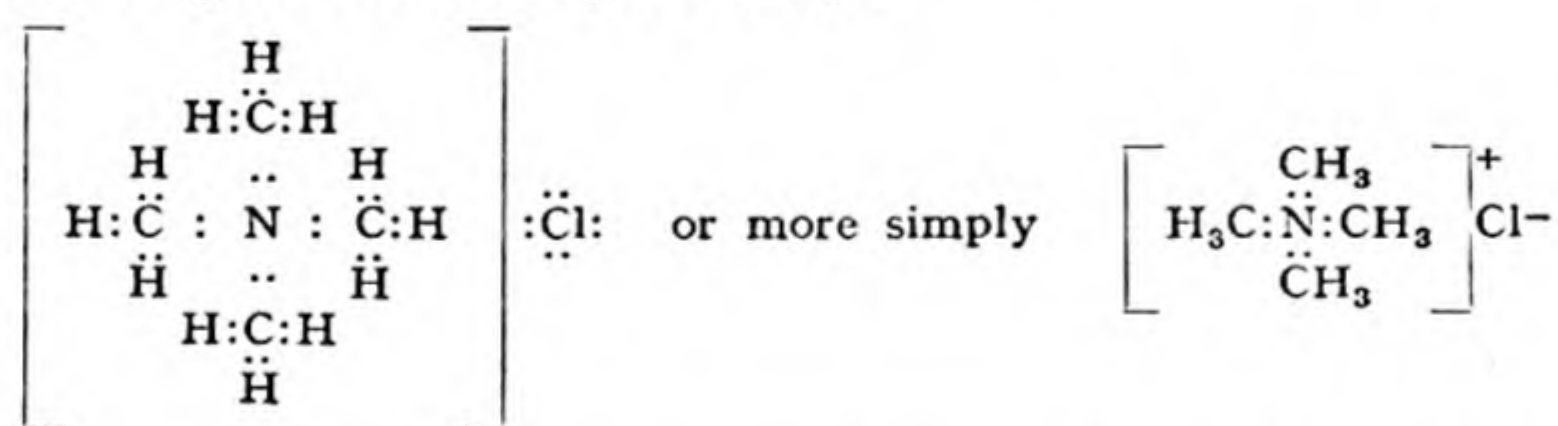
strongly basic. The presence of bases such as $[\text{H}_3\text{CNH}_3]\text{OH}$, $[(\text{H}_3\text{C})_2\text{NH}_2]\text{OH}$, etc. may be assumed in solutions of primary, secondary and tertiary amines. While ammonium hydroxide, NH_4OH , is not known in a free state, quaternary ammonium bases, $[\text{N}(\text{C}_n\text{H}_{2n+1})_4]\text{OH}$, in which the four hydrogen atoms in the NH_4 -group are replaced by alkyl residues, are crystalline compounds, stable at ordinary temperatures. The quaternary ammonium bases are dissociated in solution into OH -ions and $\text{N}(\text{C}_n\text{H}_{2n+1})_4$ -ions; these solutions are strongly alkaline.

The table below gives the degree of dissociation of some ammonium bases determined from measurements on the velocity of hydrolysis of methyl acetate and expressed against the degree of dissociation of $\text{LiOH} = 100$.

LiOH	100
NaOH	98
$[\text{N}(\text{C}_2\text{H}_5)_4]\text{OH}$	75
$[\text{N}(\text{C}_2\text{H}_5)_3\text{H}]\text{OH}$	14
$[\text{N}(\text{C}_2\text{H}_5)_2\text{H}_2]\text{OH}$	16
$[\text{N}(\text{C}_2\text{H}_5)\text{H}_3]\text{OH}$	12
$[\text{NH}_4]\text{OH}$	2

In the electrolysis of tetraethylammonium chloride in liquid ammonia at -78° the liquid around the cathode assumes a deep blue colour, which is also observed when an alkali metal is dissolved in liquid ammonia at low temperatures. If iodine is added to this blue liquid, *tetraethylammonium iodide* is produced. It is assumed therefore that the radical $\text{N}(\text{C}_2\text{H}_5)_4$ has been formed (SCHLUBACH).

The electronic formulae of quaternary ammonium salts and quaternary ammonium bases are written in the same way as those for ammonium salts and ammonium hydroxide respectively:



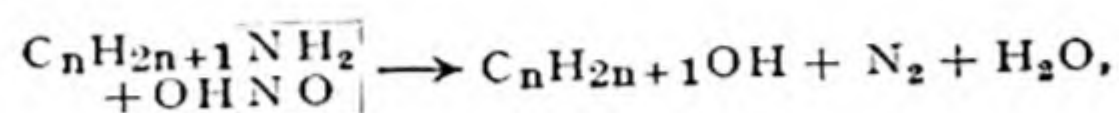
Each of the four pairs of electrons belong both to the alkyl residue and to the N-atom; since each CH_3 -group has one valency electron available and a N-atom carries 5 electrons in the outer shell, in the formation of a tetramethylammonium ion an electron is given up and taken by the chlorine atom or the oxygen atom of the OH -group, respectively. As a result, the chlorine atom is converted into a chloride ion and the OH -group into an OH -ion. In the ammonium ion the nitrogen atom has eight electrons in the outer shell so that the octet of electrons has been completed. Thus it is not possible for a nitrogen atom to be combined homopolarly with five monovalent groups. A compound such as $\text{N}(\text{CH}_3)_5$ does not exist. In the

organic quaternary ammonium compounds four bonds on the N-atom are homopolar, the fifth is heteropolar.

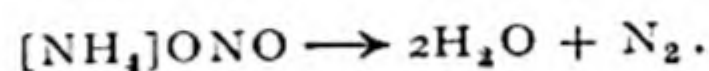
The stereochemistry of the amines and the quaternary ammonium salts is dealt with in 139.

48. Properties. Primary, secondary and tertiary amines are distinguished by their different behaviour towards nitrous acid.

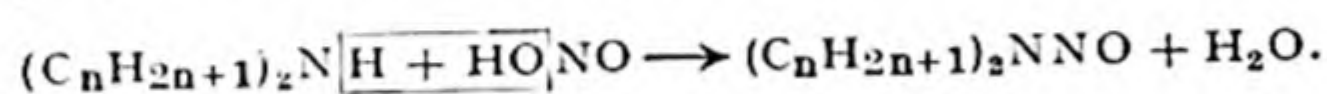
Primary amines react with this acid giving the corresponding primary alcohol with evolution of nitrogen:



a process which is exactly similar to the decomposition of ammonium nitrite into water and nitrogen



With secondary amines nitrous acid gives *nitrosamines*:



The lower members are pale yellow coloured liquids, sparingly soluble in water, which are readily converted into the secondary amine again by concentrated hydrochloric acid. The structure given above follows from this reaction; if the nitroso group were attached to carbon, either by its oxygen or by its nitrogen atom, it would no longer be possible to recover the secondary amine in this way.

Tertiary amines do not react with nitrous acid at ordinary temperatures.

This behaviour towards nitrous acid provides a means of differentiating the three classes of amines.

Another method of recognising primary, secondary and tertiary amines as such, consists of determining how many alkyl groups the amine can take up on further alkylation; *e.g.* if a compound $\text{C}_3\text{H}_9\text{N}$ is propylamine, $\text{C}_3\text{H}_7\text{NH}_2$, on warming with methyl iodide it will give a compound $[\text{C}_3\text{H}_7-\text{N}\equiv(\text{CH}_3)_3]\text{I}$, *i.e.*

$\text{C}_6\text{H}_{10}\text{NI}$; if $\text{C}_3\text{H}_9\text{N}$ were $\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{C}_2\text{H}_5 \diagup \end{array} \text{NH}$, the same treatment would give $[\text{C}_2\text{H}_5-\text{N}\equiv(\text{CH}_3)_3]\text{I}$ *i.e.* $\text{C}_5\text{H}_{14}\text{NI}$; if $\text{C}_3\text{H}_9\text{N}$ were equivalent to $(\text{CH}_3)_3\text{N}$, then $(\text{CH}_3)_4\text{NI}$ or $\text{C}_4\text{H}_{12}\text{NI}$ would be obtained. By analysing the quaternary ammonium iodide produced (I determination), it may be found whether $\text{C}_3\text{H}_9\text{N}$ is a primary, secondary or tertiary amine.

49. The first and second members of the series, *methylamine* and *ethylamine*, are inflammable gases, which are extremely soluble in water; for example 1 l of water dissolves 1150 l of methylamine gas, at 12.5° . Succeeding members have low boiling points and are miscible with water

in all proportions. They have a peculiar ammoniacal odour (of boiled crayfish). The spec. grav. of the amines is very much smaller than 1; that of methylamine, for example, is only 0.699 at -11° .

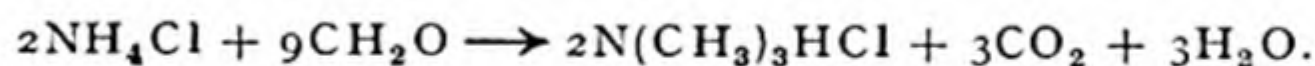
TABLE 13
MELTING AND BOILING POINTS OF SOME AMINES

Alkyl	primary		secondary		tertiary	
	m.p.	b.p.	m.p.	b.p.	m.p.	b.p.
Methyl	— 92.5°	-6.5°	-96.0°	7.4°	-124°	3.5°
Ethyl	— 80.6°	16.6°	-50°	55.5°	-114.8°	89.5°
Propyl	— 83°	48.7°	-39.6°	110.7°	— 93.5°	156°
isoPropyl	-101.2°	34°	—	84°	—	—
Butyl	— 50.5°	77.8°	—	159°	—	214°
isoButyl	— 85.5°	68°	-77°	$139-140^{\circ}$	— 21.8°	191.5°
Amyl	— 55°	104°	—	—	—	$240-245^{\circ}$

Table 13 gives the melting points and boiling points of some of the amines. Both the melting and the boiling point are lowered by branching in the alkyl group. Also trimethylamine, $(\text{CH}_3)_3\text{N}$, boils much lower than the isomeric *n*-propylamine or than isopropylamine (cf. the physical properties of the alcohols, p. 59).

Methylamine occurs in *Mercurialis perennis*; it can be prepared from ammonia and dimethyl sulphate. It burns with a yellow flame.

Trimethylamine is obtained by heating ammonium chloride with formaldehyde (commercial formalin) in an autoclave at $120-160^{\circ}$:



It occurs along with dimethylamine in herring pickle.

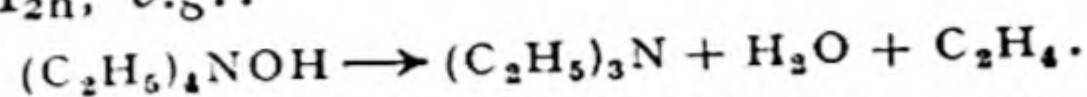
Tetramethylammonium hydroxide can be prepared from the corresponding chloride by the action of moist silver oxide; the free base crystallises in the form of hydrates which are very hygroscopic and take up carbon dioxide from the atmosphere.

The velocity of the formation of tetraalkylammonium iodides from triethylamine and an alkyl iodide or bromide was first investigated by MENSCHUTKIN. The experiments were carried out in various solvents, the mixture being heated in a sealed tube at 190° for a definite time and the amount of quaternary salt formed determined. It was found that the reaction was bimolecular and that the velocity constant k became smaller as the size of the alkyl group in the alkyl halide became greater. In the addition of propyl bromide and octyl bromide, respectively, to triethylamine in acetone as the solvent, the observed values for k were 0.00165 and 0.00110.

At the same time it was found that the nature of the solvent has a great effect on the velocity of the reaction, for a value of $k = 0.00018$ was found for the addition of ethyl iodide to triethylamine in hexane as solvent and one of $k = 0.0516$ in methanol. It has been observed that the nature of the

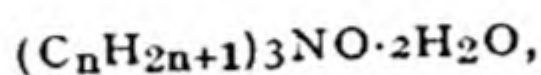
solvent has a marked influence on the velocity of the reaction in many reactions between organic substances.

Ammonium bases decompose on heating into tertiary amines, water and a hydrocarbon, C_nH_{2n} , e.g.:

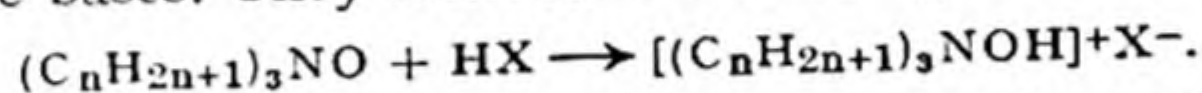


This reaction, which was discovered by HOFMANN, is generally applicable to quaternary ammonium bases; only in the very simplest, tetramethylammonium hydroxide, does the fission take another course: methanol and trimethylamine are formed.

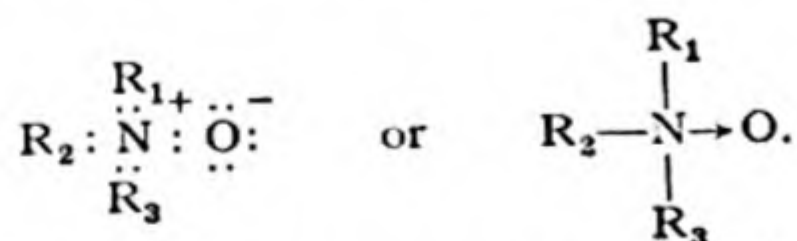
Amine oxides. These compounds are produced by the oxidation of tertiary amines with a solution of hydrogen peroxide in water; on evaporating the solution a dihydrate of the amine oxide:



is first formed, which splits off two molecules of water on gentle heating and is converted into the amine oxide $(C_nH_{2n+1})_3NO$. The amine oxides behave in aqueous solution as weak, mono-acidic bases. They form salts according to the equation:



The formulation of an amine oxide as $(C_nH_{2n+1})_3N=O$ would appear to indicate that 5 homopolar bonds emanate from the nitrogen atom or expressed otherwise, that the outer shell of the N-atom has ten valency electrons. Since no compounds are known of the type NR_5 , in which R represents an alkyl residue, and since the fifth bond of the N-atom is heteropolar in the quaternary ammonium salts or bases, the above mentioned formulation for amine oxides is not satisfactory. Another formulation can be given with the aid of the electronic theory of the chemical bond (22). The N-atom has used three valency electrons for the formation of pairs of electrons with the alkyl groups R_1 , R_2 and R_3 , each of which has one valency electron available. The lone pair of electrons of the nitrogen atom fills up the outer shell of the oxygen atom, producing a bond between N and O; both the N-atom and the O-atom now possess an octet of electrons in the outer shell. The result is, however, that the N-atom has one electron too few and the O-atom one electron too many compared with the nuclear charge; hence in the bond between N and O the N-atom is positively, and the O-atom negatively, charged. We have here a special type of bond between N and O, which is called a *semipolar bond* and which is represented by an arrow \rightarrow instead of by a bond sign $—$:



Formulae of an amine oxide with a semipolar bond.

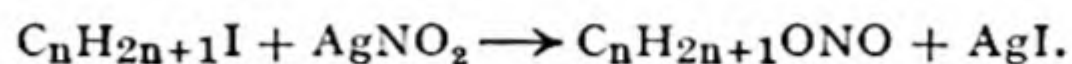
The electronic formulae of an amine oxide base $R_1R_2R_3NO \cdot H_2O$ and of an amine oxide salt $(R_1R_2R_3NOH)Br$ are represented as follows:



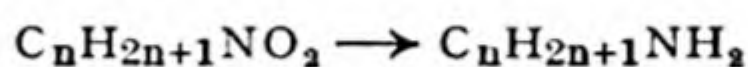
The spatial structure of the amine oxides is discussed in 139.

(b) *Nitro-compounds*

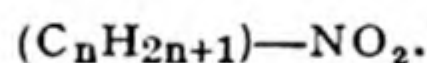
50. By interaction of silver nitrite and an alkyl iodide, two isomeric compounds of the formula $C_nH_{2n+1}NO_2$ are formed, which show a big difference in boiling point. For example, if ethyl iodide is used, one isomer boils at 17° and the other at $113-114^\circ$. The lower boiling compound is decomposed by dilute caustic soda solution into alcohol and sodium nitrite and is to be regarded, therefore, as an ester of nitrous acid, formed according to the equation:



No nitrite and alcohol is formed with alkali from the higher boiling compound; on reduction, two oxygen atoms are replaced by two hydrogen atoms and primary amines are produced:



From this last reaction, it follows, that the nitrogen must be attached directly to carbon in these compounds, because this is also the case with the amines. Since this reduction takes place even at room temperatures, the oxygen atoms are attached to nitrogen, because oxygen attached to carbon cannot be replaced by hydrogen under these conditions; oxygen-free compounds can be obtained neither from alcohols nor ethers by reduction at ordinary temperatures. It is concluded therefore that these compounds, called *nitro-compounds*, must have the structure



Thus nitro-compounds contain a grouping NO_2 , with its nitrogen atom directly attached to carbon; the group $-NO_2$ is called a nitro-group.

The names of these substances are formed by adding the prefix *nitro* to that of the saturated hydrocarbon. Thus the compound CH_3NO_2 is called *nitromethane*; $C_2H_5NO_2$ *nitroethane*; the generic name for these substances is *nitroalkanes*.

The formation of nitroalkanes from alkyl iodides and silver nitrite was discovered by VICTOR MEYER (1872); the formation of these compounds by nitrating alkanes is mentioned in 24.

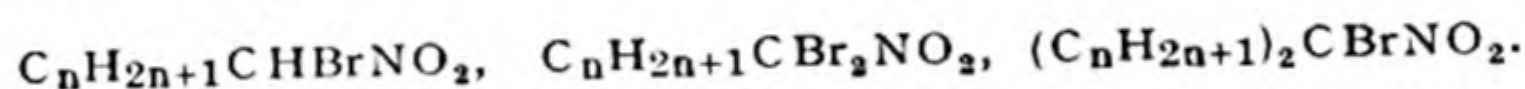
They are colourless liquids with an ethereal odour; the lower members are sparingly soluble in water. They can be distilled without decomposition.

In the primary and the secondary nitro-compounds a hydrogen atom can be replaced by alkali metal, especially by sodium. If an alcoholic solution of nitroethane is added to one of sodium alcoholate, for example, a colourless, crystalline precipitate of the composition $C_2H_4NaNO_2$ is produced.

A similar sodium compound is given also by a secondary nitro-compound such as $\text{CH}_3\text{CH}(\text{CH}_3)\text{NO}_2$, but a tertiary nitro-compound, such as $\text{CH}_3\text{C}(\text{CH}_3)_2\text{NO}_2$, does not give a sodium derivative.

These alkali derivatives of primary and secondary nitro-bodies are also produced by the action of alkalis, the nitro-compound passing into solution, since the alkali derivative is soluble in water. These alkali derivatives, when dissolved in water, show the properties of salts. The structure of these alkali salts will be discussed in 229.

From what has been said, it may already be concluded that only those nitro-compounds react with metallic sodium, or with caustic soda or sodium alcoholate, in which at least one hydrogen atom is still attached to the carbon atom carrying the nitro-group. This condition is not fulfilled in the tertiary nitro-compounds. Hence, the nitro-group has an effect on the chemical properties of the hydrogen atoms attached to the same carbon atom. This is also apparent in the behaviour of nitro-compounds towards bromine. When bromine is added to an alkaline solution of a primary or secondary nitro-compound, compounds are obtained in which one or more hydrogen atoms are replaced by bromine, *e.g.*:



Since tertiary nitro-compounds are not attacked by bromine under these conditions, it may be concluded that only those hydrogen atoms can be replaced by bromine, which are attached to the same carbon atom as the nitro-group.

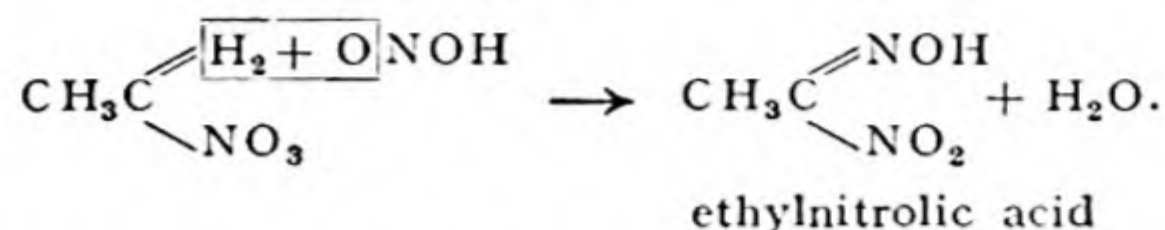
Electronic formulae of the nitro-compounds. Formulation of nitro-compounds as $\text{R}-\text{N} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{O} \end{smallmatrix}$ should indicate that the outermost shell of the N-atom is occupied by 10 valency electrons (a bond sign representing two valency electrons). It has already been explained in the case of the amine-oxides that this hypothesis is unsatisfactory. Therefore in the nitro-compounds also, it is assumed that one of the oxygen atoms in the $-\text{NO}_2$ -group is attached to the nitrogen atom by a semipolar bond; the other oxygen atom is attached by a double bond:



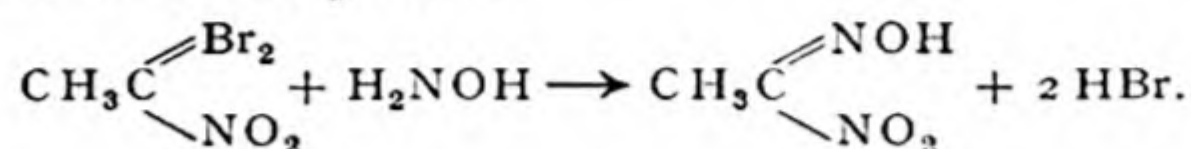
See further 139, 224.

The behaviour of nitro-compounds towards nitrous acid is important because by its means it is possible to differentiate between primary, secondary and tertiary nitro-compounds (V. MEYER). The treatment with nitrous acid is carried out by adding sodium nitrite to an alkaline solution of the nitro-compound and then adding

sulphuric acid. When this is carried out on a *primary nitro-compound*, an *alkylnitrolic acid* is produced:

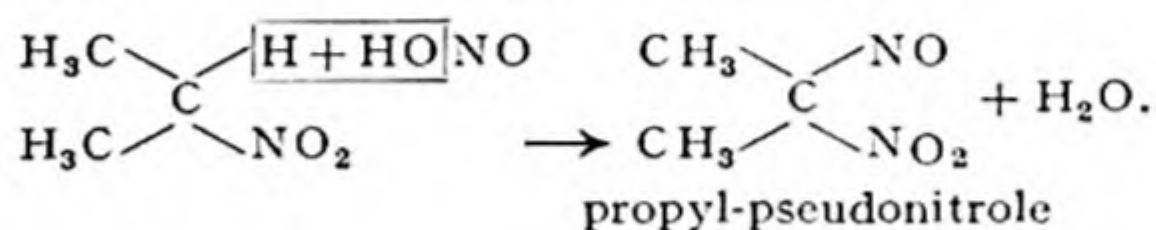


The structure of these compounds is proved by their preparation from hydroxylamine and a dibromonitro-compound:



The alkylnitrolic acids dissolve in caustic alkali with a red colour with the formation of metal compounds. This reaction is very sensitive. They are well crystallised but unstable compounds.

By this same treatment *secondary nitro-compounds* give *pseudo-nitroles*. These are compounds containing the group of atoms C(NO)(NO₂):



The pseudo-nitroles are colourless crystalline compounds, which assume a blue colour, like all compounds containing the grouping C-NO, either on melting or when dissolved. This change in colour is probably connected with polymerisation: in the blue form the substance has the simplest molecular weight, while it is present as a polymer in the colourless form; it has been observed that the molecular weight of nitroso-compounds in coloured solutions approaches the lowest possible value more closely as the colour becomes more intense.

The above mentioned reactions may also serve to distinguish primary and secondary alcohols from one another; the alcohol is converted into the corresponding alkyl iodide and then into the nitro-compound.

Tertiary nitro-compounds are unchanged by nitrous acid.

(v) ALKYL ATTACHED TO OTHER ELEMENTS

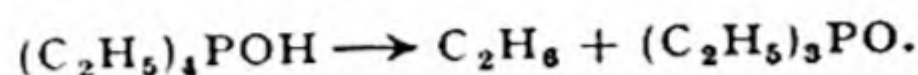
(a) Alkyl attached to elements of the nitrogen group

51. Like ammonia, phosphine (PH₃) combines with acids to form salts: the phosphonium salts (PH₄)X are decomposed into acid and phosphine by water. Arsine and antimony hydride do not form salts and show no basic characteristics. Ammonia is oxidised with difficulty and is stable towards oxygen at ordinary temperatures. Phosphine, arsine and antimony hydride are easily oxidised.

These properties are revealed also in the alkyl derivatives of these elements.

Alkylphosphines. The amines are stronger bases than ammonia; likewise the alkylphosphines are stronger bases than PH₃ and the basicity increases as more alkyl

groups take the place of hydrogen atoms. The salts of mono-alkylphosphines, for example, are still decomposed by water but those of the di- and tri-alkylphosphines are stable. The *quaternary phosphonium bases* PR_4OH are as strongly basic as the ammonium bases. When a phosphonium base is heated it does not split up into an alcohol (or $\text{C}_n\text{H}_{2n} + \text{H}_2\text{O}$) and trialkyl-compound, as do the ammonium bases, but into a hydrocarbon $\text{C}_n\text{H}_{2n+2}$ and a phosphorus compound containing oxygen:



This compound is called *triethylphosphine oxide*. The great tendency of phosphorus to combine with oxygen is clearly shown here. This is revealed also by the ease with which alkylphosphines are oxidised, which occurs even with atmospheric oxygen. When brought into contact with nitric acid, PH_3 gives phosphoric acid $\text{OP}(\text{OH})_3$; in exactly the same way the alkylphosphines take up one atom of oxygen and as many additional atoms as there are hydrogen atoms directly attached to phosphorus.

CH_3PH_2 gives $\text{CH}_3\text{PO}(\text{OH})_2$;
mono-methylphosphonic acid

$(\text{CH}_3)_2\text{PH}$ gives $(\text{CH}_3)_2\text{PO}(\text{OH})$;
dimethylphosphonous acid

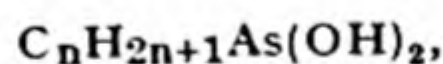
and $(\text{CH}_3)_3\text{P}$ gives $(\text{CH}_3)_3\text{PO}$
trimethylphosphine oxide

The structure of these compounds follows, for example, from the fact that *mono-alkylphosphonic acids* are dibasic, the *dialkylphosphonous acids* monobasic, and the *trialkylphosphine oxides* are devoid of acid properties.

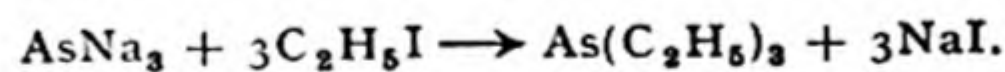
The alkylphosphines (HOFMANN, CAHOURS) are colourless liquids with a penetrating odour; methylphosphine CH_3PH_2 is a gas.

Methods of formation. Only tertiary alkylphosphines and phosphonium compounds are produced by the action of alkyl halides on PH_3 . Primary and secondary alkylphosphines are obtained by heating phosphonium iodide, PH_4I , with alkyl iodides and zinc oxide.

Arsines. Primary arsines $\text{H}_2\text{As}(\text{C}_n\text{H}_{2n+1})$ are obtained by the reduction of *mono-alkylarsinic acids*:



with zinc amalgam and hydrochloric acid. These arsines are oxidised immediately on contact with air. Tertiary arsines do not give bases with water. They are produced by the action of zinc alkyls on AsCl_3 and from arsenic-sodium and alkyl iodides:



Quaternary arsonium bases, which are produced by addition of alkyl halides to tertiary arsines and treatment of the halide obtained with silver hydroxide, have very strong basic properties.

Derivatives of dimethylarsine are called *cacodyl compounds* on account of their repulsive odour ($\kappa\alpha\kappa\omega\delta\eta\varsigma$ = stinking) and were first investigated by BUNSEN (1840). Cacodyl oxide $[(\text{CH}_3)_2\text{As}]_2\text{O}$, is produced by heating arsenious oxide with potassium acetate (CADET 1760); cacodyl chloride, $(\text{CH}_3)_2\text{AsCl}$, is produced by the action of hydrochloric acid on cacodyl oxide and can be converted by the action of zinc into cacodyl, $(\text{CH}_3)_2\text{As}-\text{As}(\text{CH}_3)_2$, m.p. -6° , b.p. 176° .

The cacodyl-group, $(\text{CH}_3)_2\text{As}-$, was considered by BUNSEN as an example of a "compound radical", from which cacodyl compounds are derived.

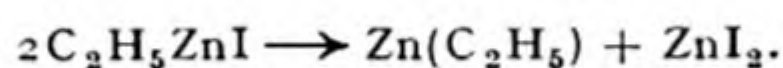
(b) *Alkyl derivatives of silicon*

52. Of the elements of the fourth main group of the periodic system silicon shows the closest similarity to carbon, a fact which is demonstrated in the *alkylsilanes*. *Tetramethylsilane* $\text{Si}(\text{CH}_3)_4$ is prepared from SiCl_4 and methylmagnesium bromide (54). It boils at 26° and is insoluble in water. The tetra-alkylsilanes, $\text{Si}(\text{C}_n\text{H}_{2n+1})_4$, show great similarity to the quaternary hydrocarbons $\text{C}(\text{C}_n\text{H}_{2n+1})_4$; they are not attacked by either nitric acid or sulphuric acid at ordinary temperatures. One or more hydrogen atoms may be substituted by the action of chlorine.

(c) *Alkyl attached to metal*

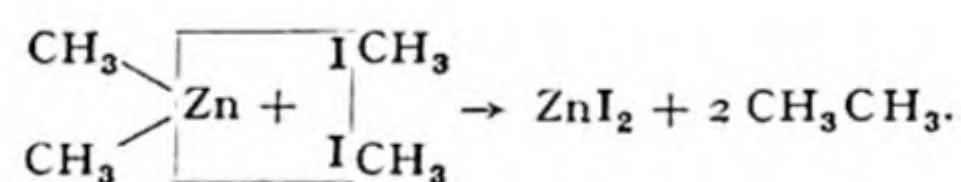
53. Alkyl compounds of most of the metals are known. Only a few, however, including the alkyl compounds of zinc, which were investigated by FRANKLAND (1855), will be discussed here.

On warming ethyl iodide with zinc, a white, crystalline compound, $\text{C}_2\text{H}_5\text{ZnI}$, ethylzinc iodide, is first produced and on heating more strongly this is decomposed into ZnI_2 and $\text{Zn}(\text{C}_2\text{H}_5)_2$:



The *dialkylzinc* is distilled from the mixture; this must be carried out in an apparatus from which the air has been displaced by nitrogen since the zinc alkyls, especially the lower members, are spontaneously inflammable in air.

The dialkylzinc compounds are colourless liquids, heavier than water. When they are allowed to react with alkyl iodides, *saturated hydrocarbons* (17) are produced:



Halogens react very violently with dialkylzinc with the formation of alkyl halides; zinc alkyls are decomposed by water into the corresponding hydrocarbon and zinc hydroxide.

The zinc alkyls have low boiling points; $\text{Zn}(\text{CH}_3)_2$ boils at 46° ; $\text{Zn}(\text{C}_2\text{H}_5)_2$ at 118° . FRANKLAND was able to determine the vapour density of these compounds and therefore to establish the molecular formula. From this it follows that zinc is divalent in these compounds; FRANKLAND's researches on the metal alkyls were of great importance for the development of the theory of valency.

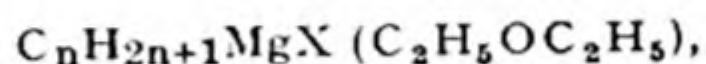
Sodium alkyls are obtained by the action of sodium on mercuri-dialkyls (SCHLENK) or by the action of sodium on alkyl chlorides in petroleum ether at low temperatures. In this way $\text{C}_4\text{H}_9\text{Na}$, $\text{C}_8\text{H}_{17}\text{Na}$, etc., have been prepared.

They are amorphous powders, which take fire in the air and are insoluble in inert solvents.

Lithium alkyls are prepared in a similar manner from lithium and alkyl halides (ZIEGLER); these compounds (with the exception of LiCH_3) are soluble in petroleum ether or benzene and are used in syntheses.

The alkyl compounds of mercury, lead, tin and several other metals are stable towards water and oxygen. The mercury and lead compounds are poisonous. On the use of *tetraethyllead*, $\text{Pb}(\text{C}_2\text{H}_5)_4$, a colourless substance, as an "antiknock agent" see 26.

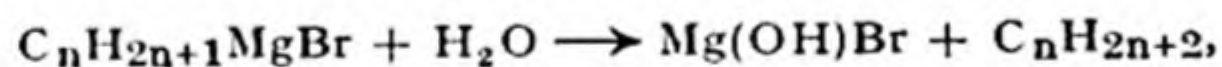
54. Alkylmagnesium compounds. When magnesium turnings are brought into contact with a completely dry ethereal solution of an alkyl halide (1 grammolecule $\text{C}_n\text{H}_{2n+1}\text{X}$ to 1 gram-atom Mg) a reaction takes place with the evolution of heat by which the metal passes into solution with the formation of $\text{C}_n\text{H}_{2n+1}\text{MgX}$. When the ether is distilled off at the end of the reaction, an addition product of alkylmagnesium halide with a molecule of ether,



remains behind.

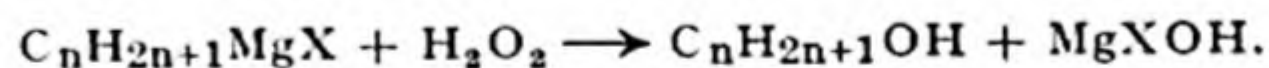
The compounds RMgX ($\text{X} = \text{halogen}$) can be obtained free from ether however, if the alkyl halide is mixed with another solvent (benzene, petroleum ether, etc.), magnesium is then added and the reaction initiated by the addition of small quantities of a tertiary amine or ether, which act catalytically.

These alkylmagnesium halides, which were discovered by V. GRIGNARD (1901), are of very great importance for a number of chemical syntheses. They are only slightly oxidisable and therefore noninflammable in air and need not be isolated but can be used for all kinds of reactions in ethereal solution. The following reaction occurs with water:



whereby saturated hydrocarbons are produced (17).

Primary alcohols are produced with hydrogen peroxide (28):



Various other examples of syntheses with alkylmagnesium halides will be given later, e.g. for the formation of acids (66) and of secondary and tertiary alcohols (59).

In general, the formation of alkylmagnesium halides takes place much more easily with alkyl bromides or iodides than with alkyl chlorides.

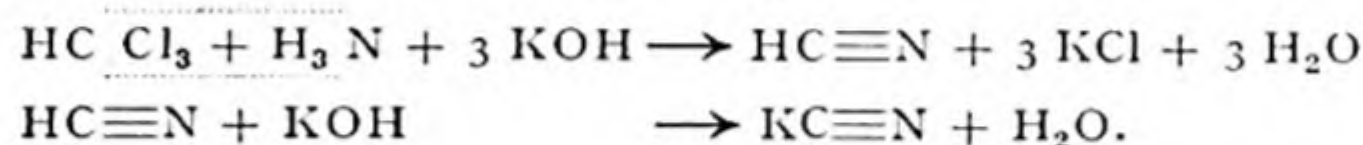
Dialkylmagnesium compounds $(\text{C}_n\text{H}_{2n+1})_2\text{Mg}$ can be obtained by the action of magnesium on the alkyl derivatives of mercury (GILMAN); they are not used for chemical syntheses.

(vi) HYDROGEN CYANIDE, CARBONITRILES AND CARBYLAMINES

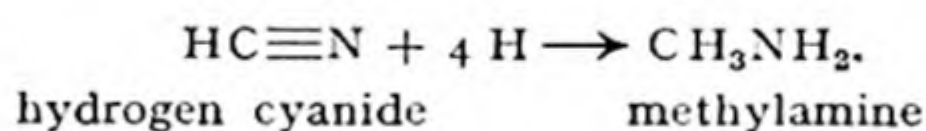
55. This chapter will deal in the first place with compounds in which the cyano group, $\text{—C}\equiv\text{N}$, occurs; these are closely related to the mono-basic alkane carboxylic acids (66).

Hydrogen cyanide, hydrocyanic or prussic acid, HCN , is produced from the elements when a mixture of nitrogen and hydrogen is passed over red hot carbon. An equilibrium is set up, the mixture containing 4.6 % of HCN at 2150° and 1 atmosphere pressure. This reaction is endothermic; the heat of formation (14) of HCN from the elements is —30 kcal .

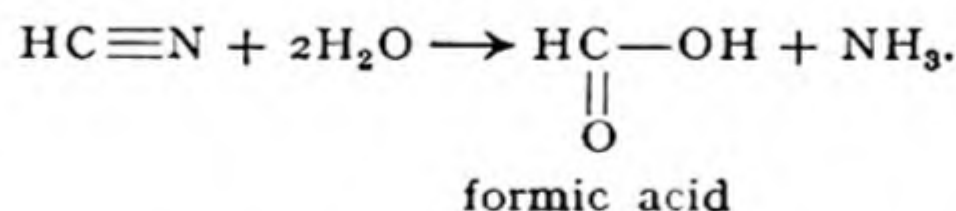
The structure of hydrogen cyanide follows from the formation of the potassium salt of this compound by warming together chloroform, alcoholic ammonia and potassium hydroxide:



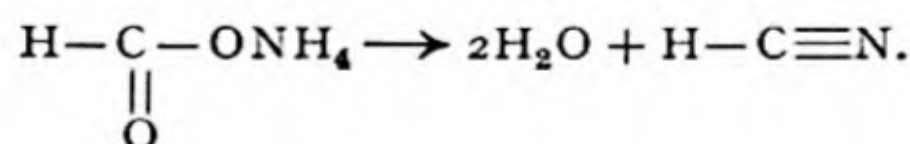
On the basis of this reaction it is assumed that the grouping $\text{—C}\equiv\text{N}$ occurs in hydrogen cyanide, in which the carbon atom and the nitrogen atom are joined by a triple bond. The idea of the multiple bond is discussed in greater detail in the chapter on alkenes (81). It will be mentioned at this stage, however, that molecules in which a multiple bond occurs, are able to undergo addition reactions by which the multiple bond is converted into a single bond. Thus hydrogen cyanide can be converted into methylamine by reduction (49):



On warming with water, hydrogen cyanide undergoes slow decomposition with the formation of formic acid (69) and ammonia (ammonium formate):

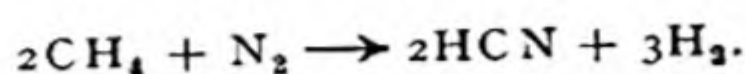


Conversely, hydrogen cyanide is produced in the dry distillation of ammonium formate. In this reaction two molecules of water are split off:



In the laboratory, hydrogen cyanide is prepared by warming potassium ferrocyanide (yellow prussiate of potash) with dilute sulphuric acid; a solution of hydrogen cyanide in water distils over, a fact observed as long ago as 1783 by SCHEELE.

Other methods of making hydrogen cyanide include the interaction of nitrogen and acetylene (91) in the electric discharge (BERTHELOT) or of nitrogen and methane (or its homologues) in a high tension electric arc:



Hydrogen cyanide is a colourless liquid with a faint odour; boiling point 25° , setting point -13.4° , spec. grav. 0.679 at 18° .

In the completely pure state, this compound can be kept unchanged for long periods but in presence of traces of water or ammonia it rapidly decomposes with the formation of amorphous products. Hydrogen cyanide shows the properties of a very weak acid. In aqueous solution, hydrocyanic acid is slowly decomposed at ordinary temperatures into amorphous, insoluble substances, as well as ammonium formate.

The composition and the vapour density of hydrogen cyanide were first determined in 1815 by GAY-LUSSAC, who obtained this substance in an anhydrous condition by the action of hydrogen chloride on mercuric cyanide. GAY-LUSSAC considered hydrogen cyanide as a compound of one atom of hydrogen with a univalent group built up of carbon and nitrogen; he also pointed out the analogy with hydrogen halides. Indeed the salts of hydrocyanic acid closely resemble the salts of halogen hydrides in some reactions.

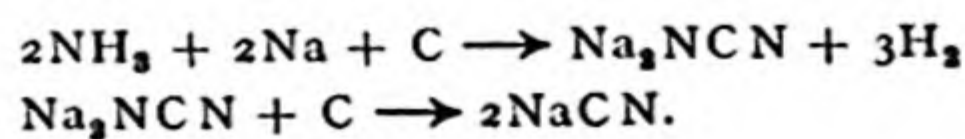
To the group $-\text{C}\equiv\text{N}$, GAY LUSSAC gave the name cyanogen, *i.e.* blue compound forming, because the pigment Prussian Blue contains this group. The name prussic acid is derived from the same source.

Later on, the name *cyano-group* came into use for the group $-\text{C}\equiv\text{N}$; this group is sometimes represented by the symbol Cy. Its similarity to the halogens is particularly apparent from the properties of dicyanogen $(\text{C}\equiv\text{N})_2$, which are discussed in 120.

Hydrocyanic acid is a very dangerous poison, both when breathed and when introduced into the blood stream, which acts fatally even in very small quantities. It is used for combatting noxious insects and rats (*e.g.* in ships' holds). It occurs in the free state in some plants *e.g.* in the seeds of the Javanese tree *Panguim edule*.

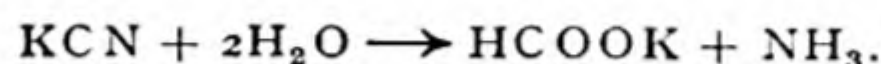
Salts of hydrocyanic acid. The cyanides of the alkali metals, those of the alkaline earth metals and mercuric cyanide, are soluble in water. The alkali salts are used in industry for extracting gold and silver from their ores and in electro-plating.

Sodium cyanide NaCN is prepared by heating charcoal with sodium in a stream of ammonia at $500-600^\circ$. Sodium cyanamide Na_2CN_2 (155) is first formed, which at the higher temperature takes up carbon and is converted into NaCN:



Sodium cyanide is also obtained by heating sodium carbonate with carbon and iron as a catalyst, in a stream of nitrogen. The carbonate is first reduced to sodium, which forms a carbide (Na_2C_2). This compound takes up nitrogen at the temperature of the reaction (about $1,000^\circ$) and cyanide is formed.

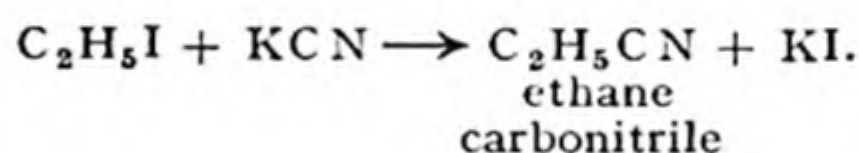
Sodium and potassium cyanides react with two molecules of water, slowly at room temperatures but fairly rapidly at the boiling temperature, to form sodium and potassium formate, respectively, with the evolution of ammonia:



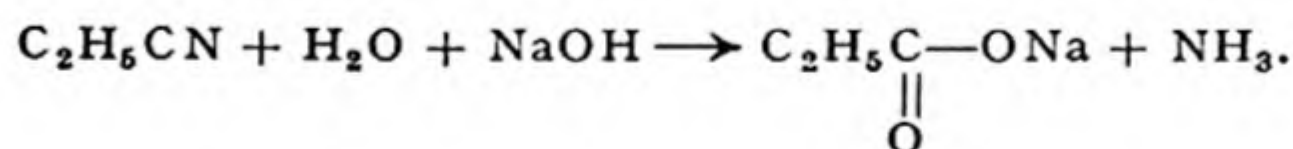
Aqueous solutions of alkali cyanides react strongly alkaline. They are decomposed by carbon dioxide in the air with the formation of carbonates and hydrocyanic acid; consequently alkali cyanides always smell of prussic acid.

Both sodium and potassium cyanides are virulent poisons.

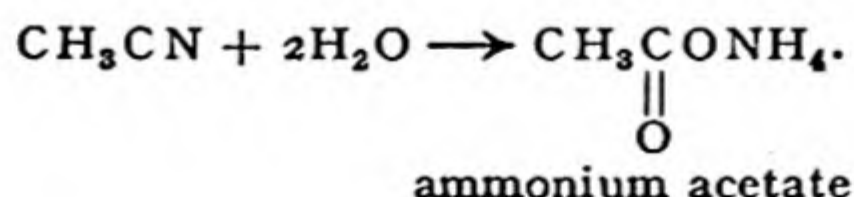
56. Carbonitriles and carbylamines (isocarbonitriles). The *carbonitriles*, compounds of the general formula $\text{C}_n\text{H}_{2n+1}\text{CN}$, are produced as the main product on heating a mixture of alkyl iodide and potassium cyanide (WILLIAMSON 1854):



Ethane carbonitrile is also formed as the main product on heating a mixture of potassium ethylsulphate and potassium cyanide or potassium ferrocyanide. In both cases a compound isomeric with the carbonitrile, viz. *ethylcarbylamine*, is produced as a by-product. The carbonitriles are split up with the absorption of a molecule of water on warming with dilute alkali; besides ammonia the alkali salt of an alkane-carboxylic acid with the same number of carbon atoms as the original nitrile is produced:



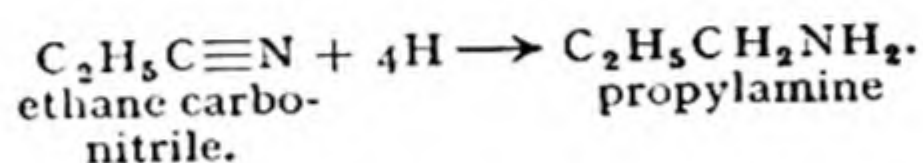
This reaction is termed *saponification* or *hydrolysis* of carbonitriles. Hydrolytic fission of carbonitriles can also be brought about by boiling with dilute acids, two molecules of water being taken up to produce the ammonium salt of the alkane carboxylic acid:



Both transformations are analogous to the conversion of hydrogen cyanide or potassium cyanide into ammonium formate or potassium formate, respectively, and ammonia. Therefore the structure $\text{—C}\equiv\text{N}$ is given to the CN-group in the carbonitriles, hence these compounds can be represented by the general formula $\text{C}_n\text{H}_{2n+1}\text{C}\equiv\text{N}$.

The carbon atoms in the molecule of a carbonitrile form a carbon chain therefore, in agreement with the fact that they are converted into carboxylic acids with the same number of carbon atoms by acid or alkaline hydrolysis. With regard to an intermediate product in this hydrolysis see 66.

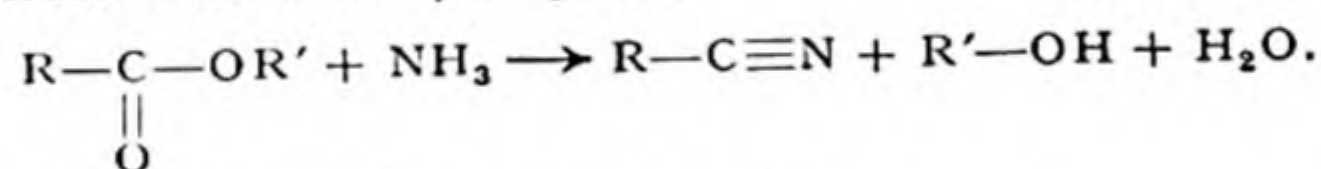
On account of the triple bond the group $\text{—C}\equiv\text{N}$ can take part in addition reactions. When carbonitriles are reduced by means of alcohol and sodium, primary amines with the same number of carbon atoms are produced (MENDIUS) (46):



On other addition products of carbonitriles see 58.

In the catalytic reduction, either with nickel in the vapour phase or with platinum at ordinary temperatures, secondary amines are produced along with the expected primary amines.

Carbonitriles may also be obtained by passing esters mixed with ammonia over aluminium or thorium oxide at $480\text{--}500^\circ$:



For other methods of formation see 78, 59.

The carbonitriles are named after the alkane from which they are derived; CH_3CN *methane carbonitrile*, $\text{C}_4\text{H}_9\text{CN}$, *butane carbonitrile*, etc. They are also named after the acids they produce on hydrolysis, thus: CH_3CN is *acetonitrile*, $\text{C}_2\text{H}_5\text{CN}$ *propionitrile*, etc. and they are frequently referred to as *alkyl cyanides*.

The lower members of the series are colourless liquids, fairly readily soluble in water; they are good solvents for various inorganic salts; they possess a faint, not unpleasant odour. The carbonitriles have weakly basic properties.

Table 14 gives some of the physical constants of carbonitriles with normal carbon chains (BRUYLANTS, see also 23).

Carbylamines or *isocarbonitriles* $\text{C}_n\text{H}_{2n+1}\text{NC}$. These compounds were obtained in 1866 by GAUTIER by the action of alkyl iodides on silver cyanide. In this reaction the isomeric carbonitriles were obtained as by-products (compare the method of preparation of the carbonitriles on p. 95). When alcoholic potash is allowed to react on a mixture of a primary amine and chloroform, carbylamines are the sole products (HOFMANN):

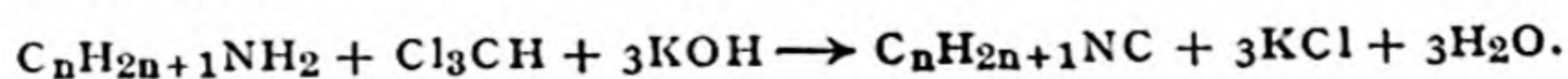
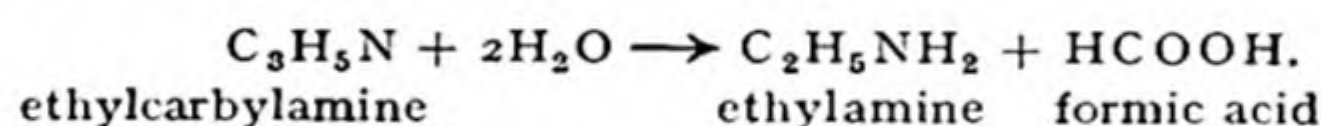


TABLE 14
SOME PHYSICAL CONSTANTS OF *n*-CARBONITRILES

	M.P. in °C	B.P. in °C/760 mms.	d_4^{15}
CH ₃ CN	— 44.9	81.6	0.7874
C ₂ H ₅ CN	— 91.9	97.3	0.7867
C ₃ H ₇ CN	—111.9	117.9	0.7954
C ₄ H ₉ CN	— 96.0	141.2	0.8035
C ₅ H ₁₁ CN	— 79.4	163.9	0.8094
C ₆ H ₁₃ CN	—	184.5	0.8135
C ₇ H ₁₅ CN	— 45.6	205.2	0.8174
C ₈ H ₁₇ CN	— 34.2	224.0	0.8206

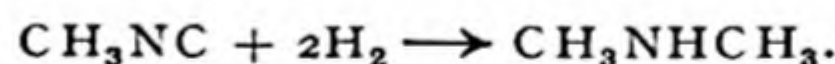
From this method of formation it follows that the C_nH_{2n+1}-group is attached directly to nitrogen in the carbylamines, so that the formula given above correctly represents these compounds. This is confirmed by the following facts.

The carbylamines are decomposed by the action of dilute acids at room temperature, two molecules of water being taken up with the formation of primary amines and formic acid:

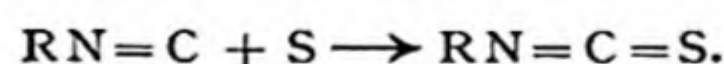


From this hydrolytic fission it follows that the C₂H₅-group is directly attached to the nitrogen atom and that the third carbon atom is not attached directly to the other two, since it is easily split off in the form of formic acid, which is expressed by the formula C₂H₅NC.

In agreement with this formula, carbylamines are easily converted into secondary amines by catalytic reduction (with nickel at about 160°):



The structure of the carbylamines can be expressed by the formula C_nH_{2n+1}N=C (NEF). This formula contains a bivalent carbon atom. This opinion is supported by the course of some addition reactions in which addition takes place only to the carbon atom of the group —NC. Thus esters of isocyanic acid are produced by the oxidation of carbylamines with mercuric oxide and esters of isothiocyanic acid (158) by the action of sulphur:



The carbylamines are liquids which are lighter than and only slightly soluble in water. They possess a very penetrating, disgusting odour, by which they can be recognised in extremely small quantities. On this account their method of formation from primary amines and chloroform

provides a *very sensitive test for primary amines*. Secondary and tertiary amines cannot be converted into carbylamines.

The lower members of the series are poisonous. The carbylamines are very reactive compounds, which can form addition compounds with many other substances. Some examples of this have already been given.

In ethereal solution they easily add on hydrogen halide so that at first these compounds were erroneously regarded as bases. This is how the name carbylamine originated. It has already been mentioned that the carbylamines are decomposed much more rapidly by dilute acids than the isomeric carbonitriles; the carbylamines are stable towards alkalis.

The carbylamines change into the isomeric carbonitriles on heating to about 200° .

The carbylamines are named after the alkyl group to which the group $-\text{N}=\text{C}$ is attached, thus *methylcarbylamine* CH_3NC , *ethylcarbylamine* $\text{C}_2\text{H}_5\text{NC}$, etc. When the isocarbonitrile terminology is used these compounds are named after the alkane from which they are derived, thus *methane isocarbonitrile* CH_3NC , etc. They are also referred to as *alkyl isocyanides*.

The boiling points of some carbylamines are given in Table 15.

TABLE 15
BOILING POINTS OF SOME CARBYLAMINES

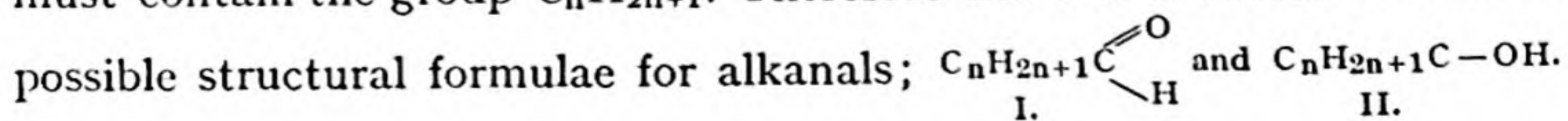
Carbylamine	B.p. in $^{\circ}\text{C}$ at 760 mms.
CH_3NC	59.6
$\text{C}_2\text{H}_5\text{NC}$	78.1
$\text{C}_3\text{H}_7\text{NC}$	99.5
$\text{C}_5\text{H}_{11}\text{NC}$	139–140

(vii) ALKANALS (ALDEHYDES) AND ALKANONES (KETONES)

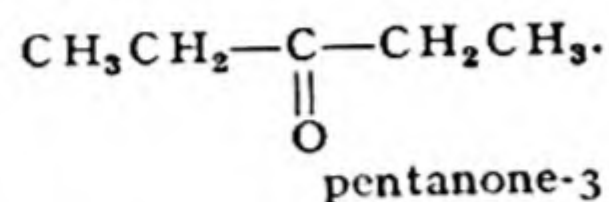
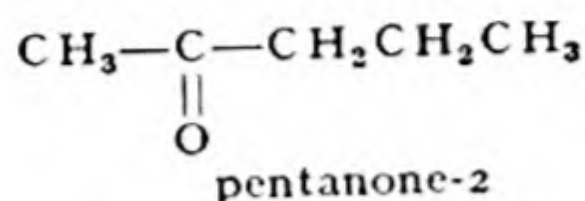
57. The general formula for these compounds is $\text{C}_n\text{H}_{2n}\text{O}$. The alkanals are produced from primary alcohols and the alkanones from secondary alcohols, by gentle oxidation *e.g.* with potassium bichromate and dilute sulphuric acid.

From the general formula for the alkanols, $\text{C}_n\text{H}_{2n+2}\text{O}$, it follows that two hydrogen atoms are removed in this oxidation.

When primary alcohols $\text{C}_n\text{H}_{2n+1}\text{CH}_2\text{OH}$ are oxidised more vigorously, acids with the formula $\text{C}_n\text{H}_{2n+1}\text{C}\begin{smallmatrix} \text{O} \\ \parallel \\ \text{OH} \end{smallmatrix}$ (66) are produced. These acids are also produced when alkanals are oxidised. Hence the molecule of an alkanal must contain the group $\text{C}_n\text{H}_{2n+1}$. Therefore there is a choice between two possible structural formulae for alkanals;

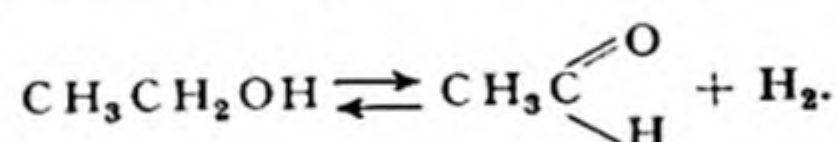


In the molecule of an alkanal the grouping $-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}$ is always a terminal group; hence, in this case, isomerism depends solely on branching of the carbon chain in the alkyl residue. In the alkanones, however, the group $>\text{C}=\text{O}$ can occupy different positions in the carbon chain so that isomerism is possible with alkanones containing 5 or more carbon atoms. The carbon atom of the carbonyl group is indicated by a number:



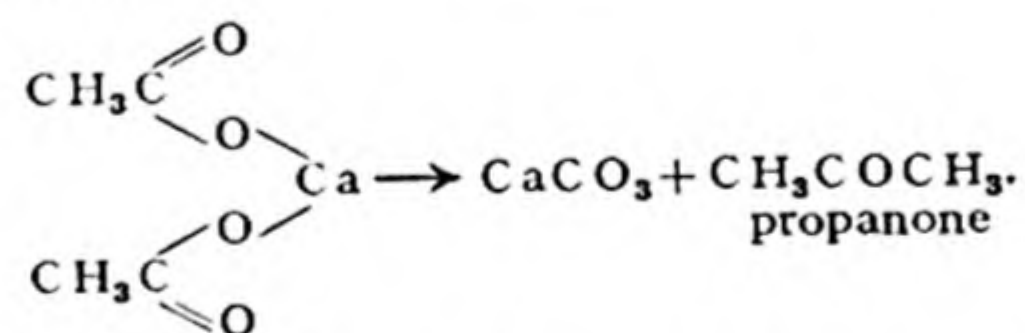
58. *Methods of preparation.* A. *For both alkanals and alkanones.* 1. The oxidation of primary and secondary alcohols to alkanals and alkanones, respectively, can be carried out by passing the alcohol, in the vapour state mixed with air, at a high temperature over catalytically active metals such as copper or platinum, as well as with potassium bichromate and dilute sulphuric acid.

SABATIER and SENDERENS have provided a very elegant method for preparing the lower alkanals. Alcohol vapour without admixed air is passed over finely divided copper at $300-350^\circ$ when hydrogen is split off as follows:

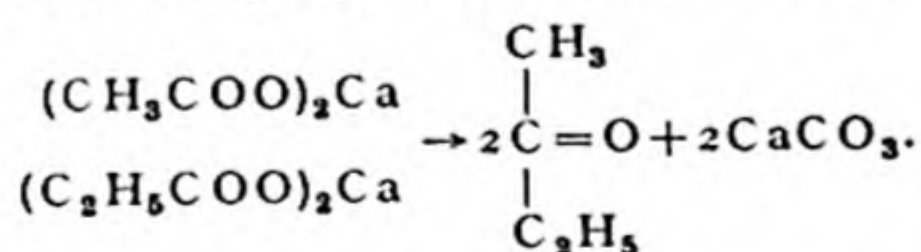


This reaction is reversible and at about 100° the equilibrium is well over on the side of the alcohol.

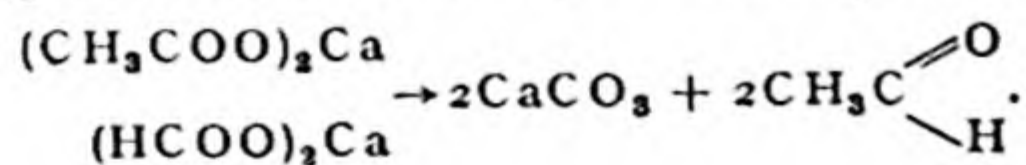
2. Alkanones are produced by heating the calcium or barium salts of alkane carboxylic acids:



If a mixture of calcium salts of two different fatty acids is used then ketones with two different alkyl groups (mixed ketones) are produced:



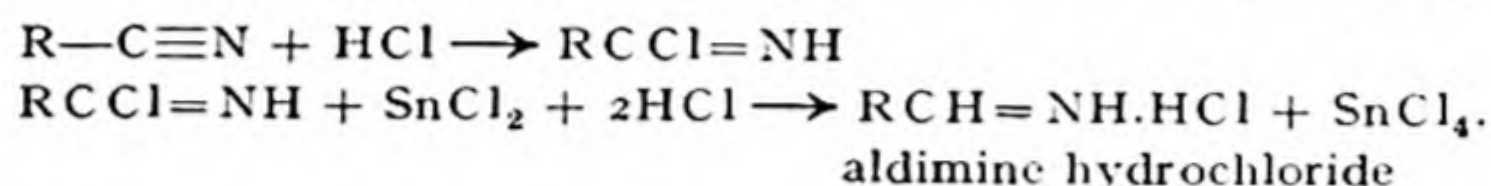
The reaction mixture also contains *acetone* and *diethyl ketone* as well as *methyl ethyl ketone*. By heating a mixture of calcium formate and the calcium salt of a homologue of formic acid, an aldehyde is produced, *e.g.*:



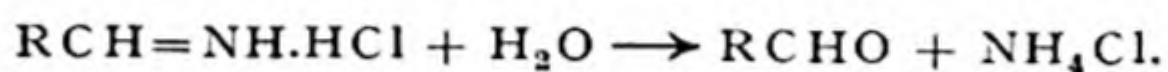
The reaction mixture also contains acetone produced from the calcium acetate and other by-products produced by the reducing action of the formate.

B. *For alkanals.* 1. Preparation by reduction of acid chlorides is mentioned on p. 99.

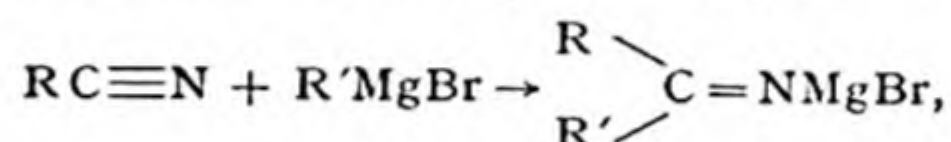
2. On treating an ethereal solution of a carbonitrile with dry hydrogen chloride and stannous chloride the following reactions take place (STEPHENS):



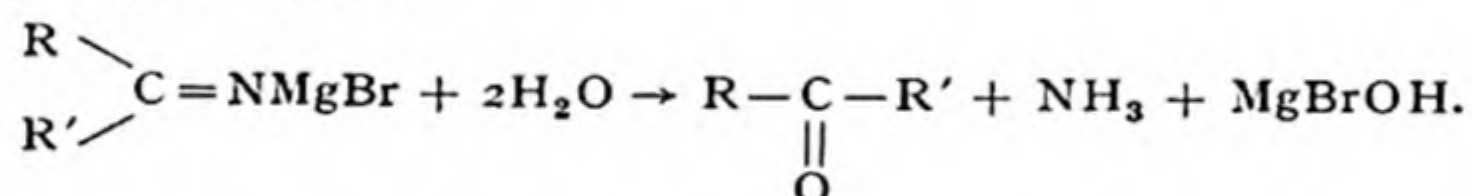
and the aldimine hydrochloride gives an alkanal on treatment with water:



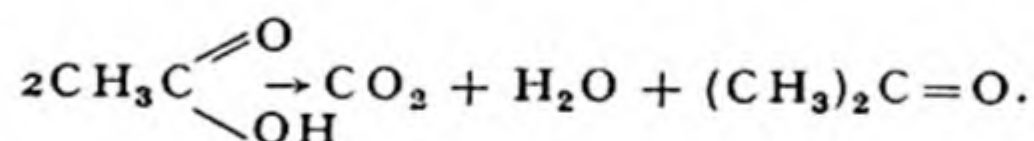
C. *For alkanones.* 1. Alkanones can be obtained by the action of alkyl-magnesium halides on carbonitriles (BLAISE):



a magnesium derivative of a ketonimide is produced from which the ketone is obtained by hydrolysis:



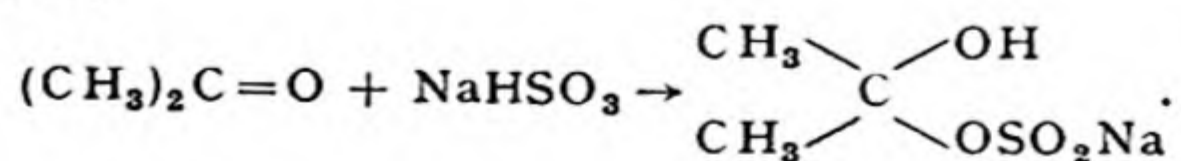
2. Ketones are produced when the vapour of acetic acid or its homologues is passed over catalytically active metallic oxides (Al_2O_3 , ThO_2 , CaO) at about 400° :



59. *Properties.* Alkanals and alkanones can combine with various substances. This *power of addition* is associated with the double bond between the carbon and the oxygen atom. In these addition reactions the double bond is converted into a single bond (see 85).

1. Addition of *hydrogen* takes place by the action of sodium amalgam on aqueous solutions of alkanals and alkanones, with the production of primary and secondary alcohols, respectively. This reduction may also be carried out catalytically with hydrogen in presence of nickel.

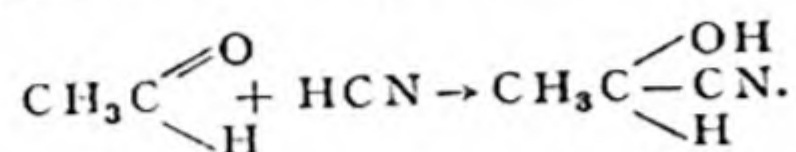
2. Addition of *sodium bisulphite*. When aldehydes or ketones are shaken with a concentrated solution of this reagent, an addition product separates in a crystalline form:



The aldehydes or ketones are liberated again from these addition products

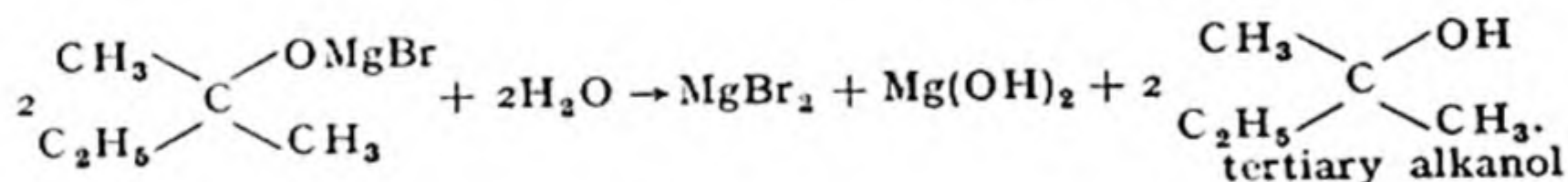
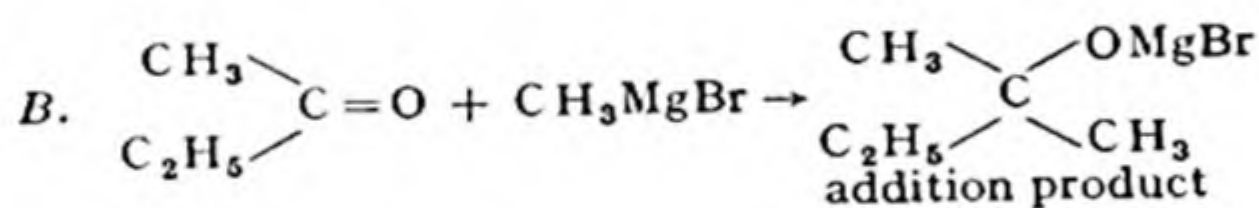
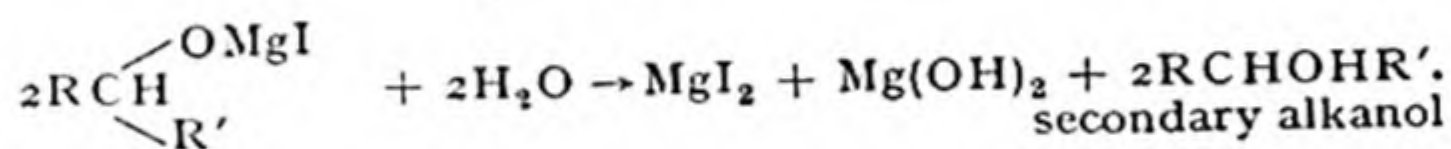
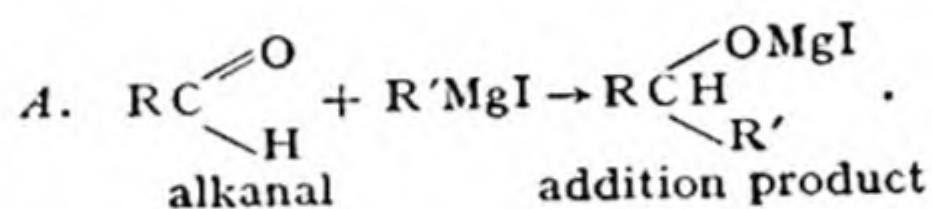
by treatment with dilute acids or with soda. The reaction is used therefore to obtain aldehydes or ketones in a pure state from mixtures with other materials.

3. Addition of *hydrocyanic acid* takes place when an aldehyde or a ketone is mixed with anhydrous hydrogen cyanide and a very small amount of an alkaline solution (*e.g.* of caustic potash or potassium cyanide in water):



Hydroxycarbonitriles or *cyanhydrins* are produced. This addition reaction is of great importance for the synthesis of hydroxy-acids (130), which are produced from the hydroxycarbonitriles by hydrolysis.

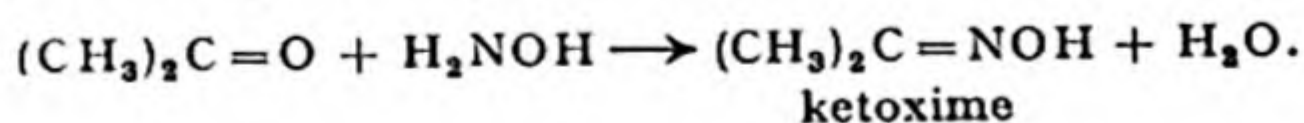
4. Addition of *alkylmagnesium halides* leads to secondary or tertiary alkanols:



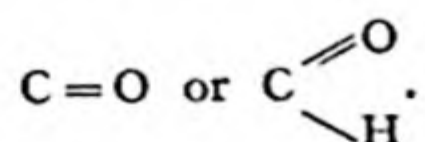
The oxygen atom in the alkanals and alkanones can be replaced by various atoms or groups of atoms.

1. Replacement by two atoms of chlorine by the action of phosphorus pentachloride is mentioned in 57.

2. The action of compounds containing the grouping —NH_2 is important. By the action of hydroxylamine, *oximes* are produced, which are called *aldoximes* (alkanaloximes) if they are derived from aldehydes and *ketoximes* (alkanone oximes) if they are formed from ketones:



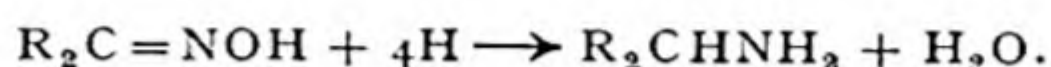
This reaction is quite general for compounds containing the groupings:



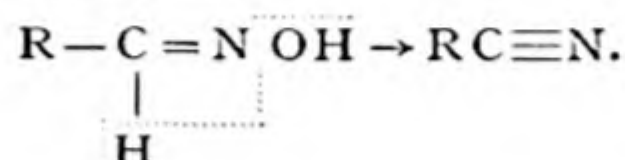
The oximes have both weakly acid and weakly basic properties; the hydrogen atom of the OH-group can be replaced by metals, consequently

the oximes dissolve in alkalis. They can also form salts with acids in the same way as ammonia. Aldehydes or ketones are regenerated from the oximes by boiling with dilute acids, water being taken up and hydroxylamine being produced at the same time.

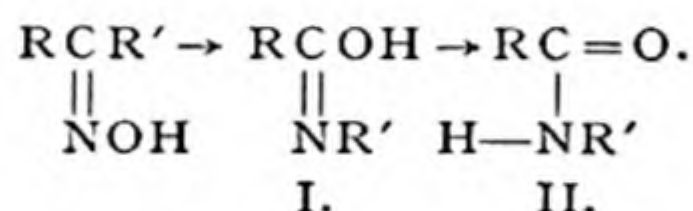
The oximes may be converted into primary amines by vigorous reducing agents:



Aldoximes are converted into carbonitriles (56) by the action of dehydrating agents like acetic anhydride:

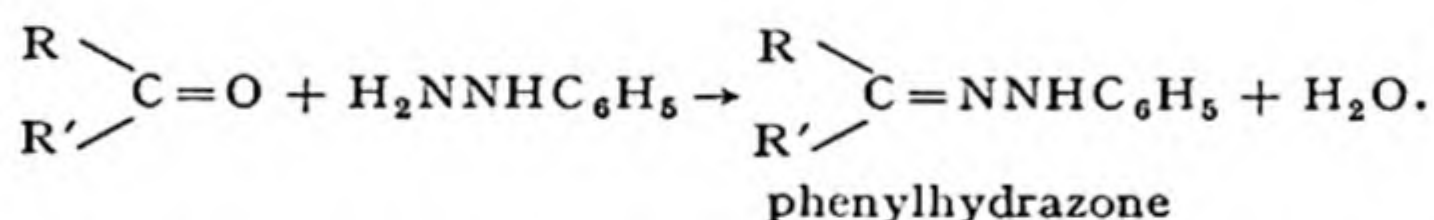


Ketoximes can be made to undergo a remarkable *intramolecular transformation* by which substituted acid amides are produced (BECKMANN transformation):



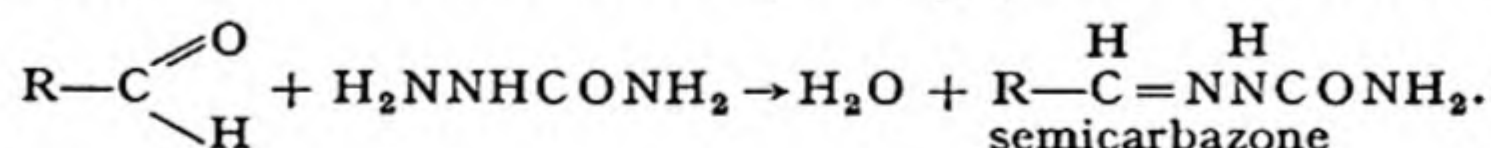
This reaction takes place under the influence of concentrated sulphuric acid or of phosphorus pentachloride; it is assumed that an unstable intermediate product I is first formed, by a change in positions of the groups OH and R', which is then transformed into the acid amide II. (compare 104).

3. By the action of phenylhydrazine (247) *phenylhydrazones* are produced (E. FISCHER):



As a rule these compounds crystallise well. On heating with hydrochloric acid they take up water and are split up into aldehyde or ketone and phenylhydrazine.

4. By the action of semicarbazide (see 152) *semicarbazones* are produced:



The aldehydes or ketones can be recovered from these compounds, which are usually well crystallised, by hydrolytic fission.

Aliphatic aldehydes and ketones show selective absorption in the ultra-violet (13); the maximum in the absorption band lies at about 2950 Å, for aliphatic aldehydes and between 2800 and 3000 Å for a number of aliphatic ketones. These absorption bands must be attributed to the C=O bond. Table 16 gives the maxima of the absorption bands for a few ketones in various solvents and without a solvent. It is seen that the maximum of the absorption band is displaced towards longer wave-lengths by substituting methyl groups.

TABLE 16
MAXIMA OF ABSORPTION BANDS IN THE ULTRA-VIOLET OF SOME KETONES

Solvent	Water	Alcohol	Hexane	No solvent
CH_3COCH_3	2640 Å	2720 Å	2790 Å	2740 Å (see fig. 20)
$\text{CH}_3\text{COCH}_2\text{CH}_3$	2665	2727	2800	2770
$\text{CH}_3\text{COCH}(\text{CH}_3)_2$	—	—	2845	—
$\text{CH}_3\text{COC}(\text{CH}_3)_3$	2760	2822	2870	2850
$(\text{CH}_3)_3\text{CCOC}(\text{CH}_3)_3$	—	2950	2950	2950 (see fig. 20)

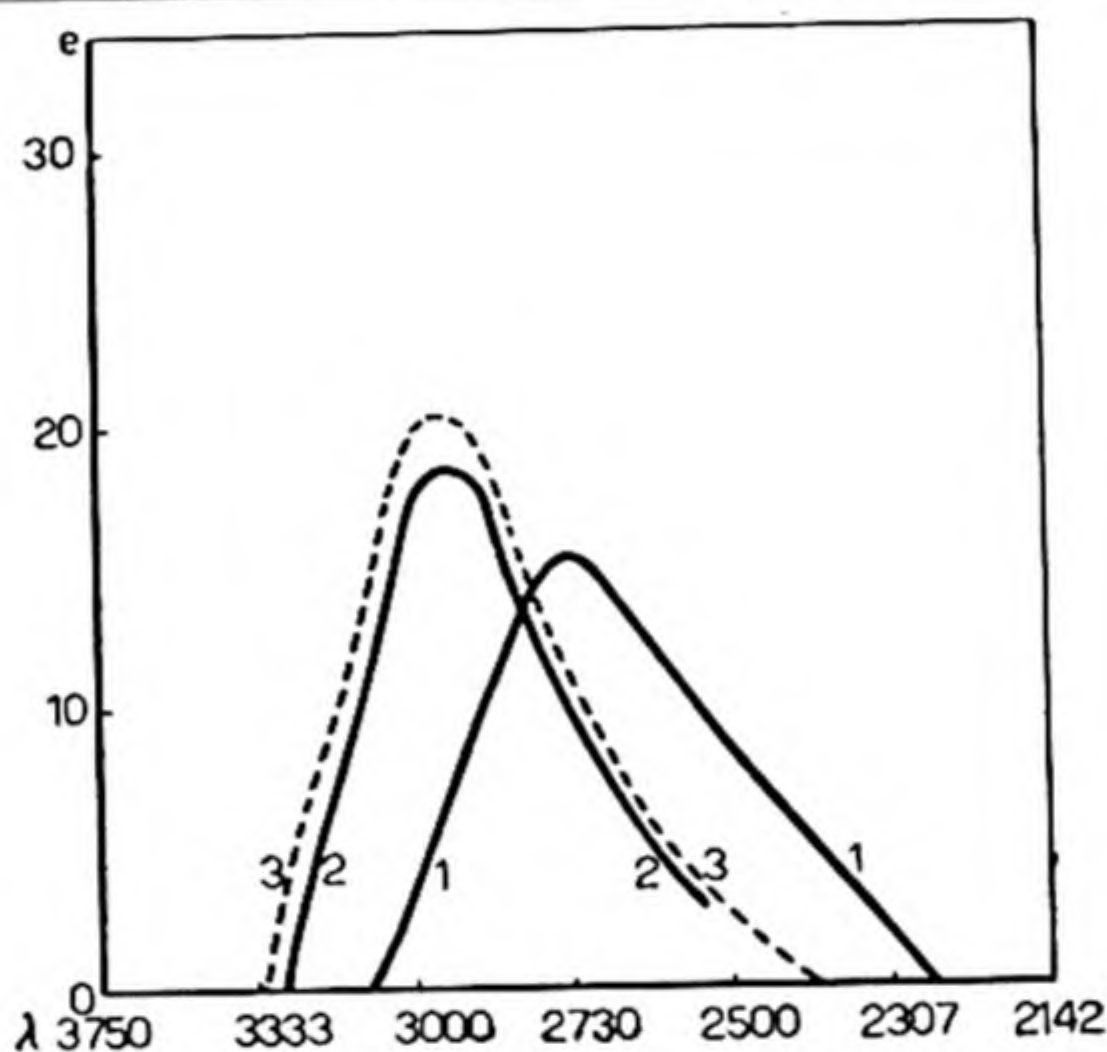


Fig. 20. Selective absorption in the ultra-violet by some aliphatic ketones
1 = acetone; 2 = pentamethylacetone; 3 = hexamethylacetone

ALKANALS (ALDEHYDES)

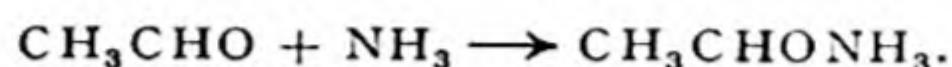
60. The melting points and boiling points of a few aldehydes are given in Table 17. The lower members are miscible with water in all proportions.

TABLE 17
MELTING AND BOILING POINTS OF SOME ALDEHYDES

Name	Formula	M.p.	B.p.
Methanal	HCHO	-118°	-19°
Ethanal	CH_3CHO	-123.3°	20.8°
Propanal	$\text{C}_2\text{H}_5\text{CHO}$	-81°	49.5° (740 mms)
Butanal	$\text{C}_3\text{H}_7\text{CHO}$		74°
Pentanal	$\text{C}_4\text{H}_9\text{CHO}$		103.4°
Heptanal (oenanthaldehyde)	$\text{C}_6\text{H}_{13}\text{CHO}$	-43.3°	152.8°
Hexadecanal (palmitaldehyde)	$\text{C}_{15}\text{H}_{31}\text{CHO}$	34°	202°

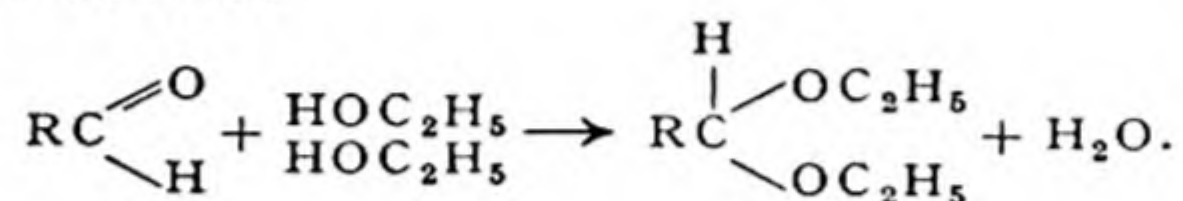
In addition to the properties which aldehydes and ketones share in common, aldehydes alone have the following special characteristics.

1. *Addition of ammonia*: this reaction takes place when liquid ammonia or a concentrated solution of ammonia in water acts, for example, on acetaldehyde:



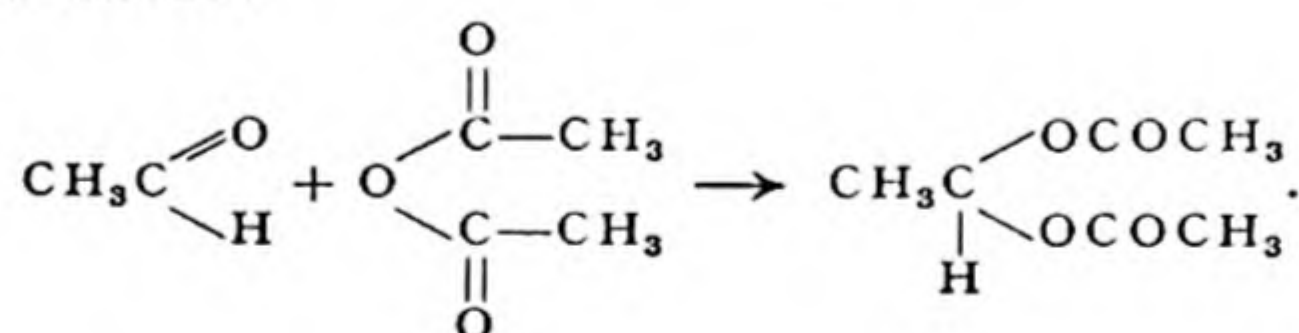
The molecular formula of acetaldehyde-ammonia is three times that of the empirical formula; these compounds are split up into their components by acids.

2. *Reaction with alcohols*:



This reaction takes place when a mixture of aldehyde, anhydrous alcohol and a little hydrogen chloride or anhydrous copper sulphate is warmed; the reaction is reversible. The compounds which are formed, *1,1-dialkoxyalkanes* or *acetals*, are liquids with a pleasant smell. The acetals are readily split up hydrolytically into alcohol and aldehyde by warming with dilute mineral acids. From this it follows that the alkyl groups are attached to the carbon atom of the aldehyde group through oxygen atoms, since a bond between carbon atoms would not be broken under these conditions. The acetals are *not* changed by dilute alkalis. Acetals are produced as by-products in the preparation of aldehydes by oxidising primary alcohols with potassium bichromate and dilute sulphuric acid.

3. *Addition of acid anhydrides*. This reaction also occurs under the influence of mineral acids:



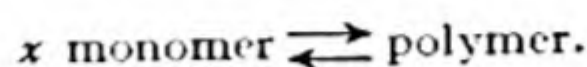
These addition products are readily split up into their components by warming with water.

4. *Polymerisation of aldehydes*. By *polymerisation* is understood a reaction in which two or more molecules of the same kind combine with each other, so that a new compound (*polymer*) is produced having the same composition as the original compound (*monomer*) but two or more times the molecular weight. If two molecules of the monomer combine, the polymer so formed is called a *dimer*, if three molecules combine, a *trimer* (μερος = part) and so on. It can also happen that a large number

of molecules of the monomer can combine to a polymer of very high and frequently unknown molecular weight.

Two distinct types are encountered in the formation of polymers:

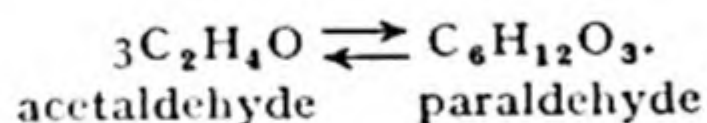
a) Where the monomer can be regenerated from the polymer without other decomposition reactions occurring, *i.e.* the polymerisation is a reversible process:



b) Where the monomer cannot be regenerated from the polymer without other decomposition reactions taking place simultaneously, *i.e.* the polymerisation is not reversible.

Polymerisation reactions also occur in which the mutual relationship between monomer and polymer does not fit precisely into the division just mentioned but stands in between the two limits. Very clear examples of both methods of polymerisation are to be found in the aldehydes, however.

61. 5. *Formation of paraldehyde from acetaldehyde.* When a small quantity of concentrated sulphuric acid is added to acetaldehyde, a violent reaction takes place with the evolution of heat; a liquid is produced, which boils at 124° (the boiling point of acetaldehyde is 20.8°) and which, from analysis and determination of the vapour density, has the formula $C_6H_{12}O_3$. This compound, called *paraldehyde* or *paraethanal*, is reconverted into acetaldehyde by distillation with dilute sulphuric acid; hence this is a reversible reaction:

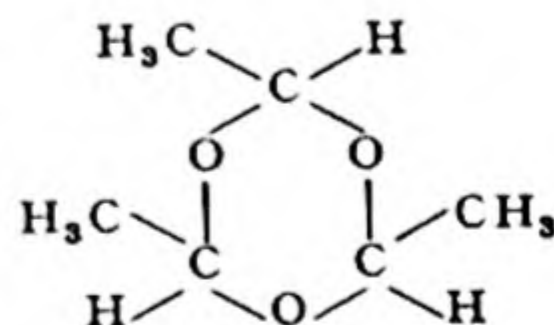


the sulphuric acid acting catalytically.

Paraldehyde no longer has the characteristic properties of aldehydes, it has no reducing power and is not resinified by alkalis. Hence the molecule

does not contain the group $-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}$; since sodium does not

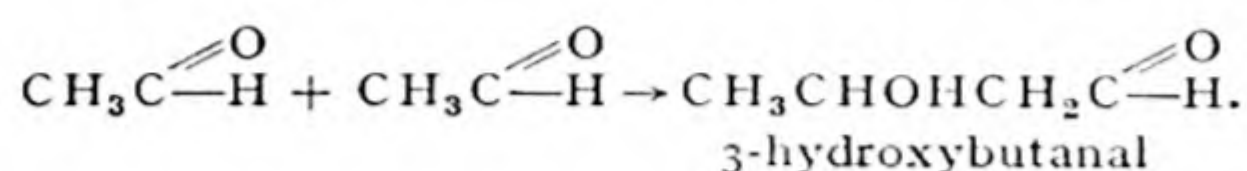
react with paraldehyde there is no OH group in the molecule. The annexed structural formula agrees with these properties. This formula also takes account of the easy disruption of paraldehyde into acetaldehyde, since this involves the breaking of bonds between carbon and oxygen only.



Besides paraldehyde another polymer of acetaldehyde is known, namely *meta-ethanal*, $[C_2H_4O]_n$, a white, crystalline compound, which is produced from ethanal under the influence of hydrochloric or sulphuric acids at low temperatures. Meta-aldehyde does not give aldehyde reactions; on warming it dissociates into acetaldehyde.

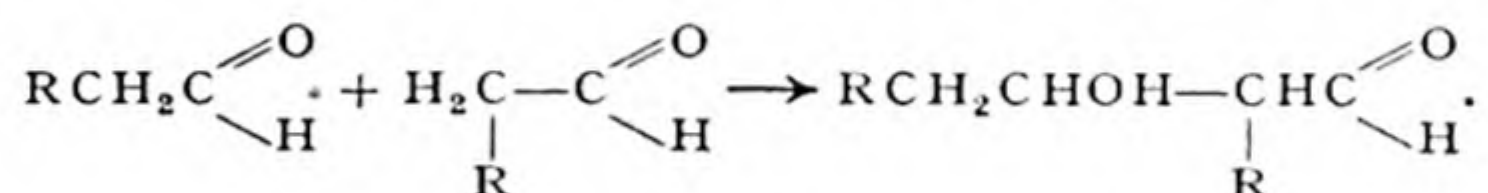
6. *Formation of aldols from aldehydes.* On treating acetaldehyde with a solution of soda or sodium acetate or with very dilute alkali, a compound

of the formula $C_4H_8O_2$ is produced. This compound, *3-hydroxybutanal* (aldol), still has the properties of an aldehyde; on oxidation it gives an acid of the composition $C_4H_8O_3$, a hydroxybutyric acid (see 131), which can be converted into butyric acid (71). Therefore a chain of four carbon atoms must be postulated in 3-hydroxybutanal. Hence the combination of two molecules of acetaldehyde to hydroxybutanal must be represented as follows:



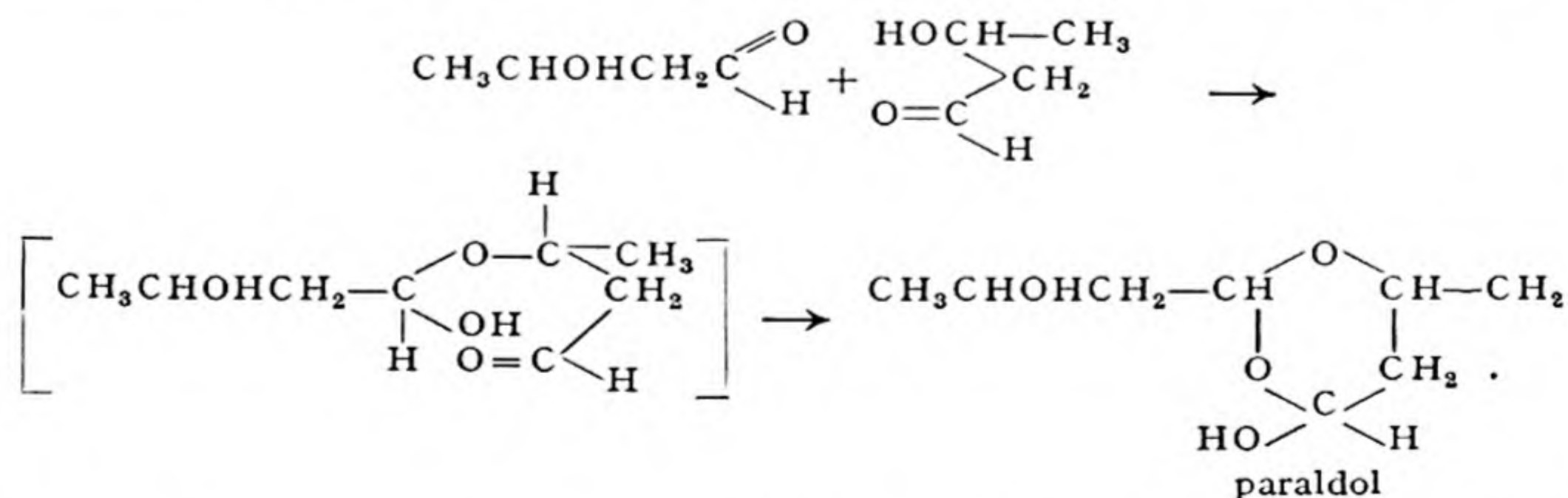
Ethanal cannot be recovered in any simple way from 3-hydroxybutanal; this is in agreement with the above structural formula. This compound has an alcohol and an aldehyde group; hence the name: *ald(ehyde-alcoh)ol*.

The formation of aldol, which is known by the simplified nomenclature of *aldol condensation*, takes place with homologues of acetaldehyde in such a way that a hydrogen atom from the CH_2 -group, which is directly attached to the aldehyde group, reacts with the aldehyde group in a second molecule:



Aldehydes of the type $R_1R_2R_3C(=O)H$, in which the carbon atom adjacent to the carbonyl group has no hydrogen atoms attached to it, do not form aldols.

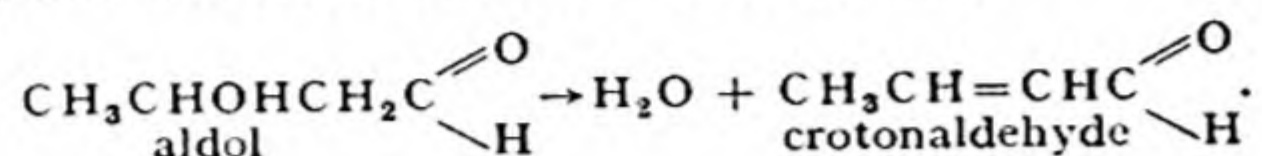
Aldols can polymerise to dimers; thus 3-hydroxybutanal produces a crystalline compound called *paraldol*, which decomposes into aldol when heated in a vacuum. The dimerisation probably takes place as follows:



When an aqueous solution of acetaldehyde is warmed with not too dilute caustic soda or caustic potash, the liquid becomes yellow in colour and a yellowish red, amorphous mass of *aldehyde resin* soon separates. This reaction is referred to as the *resinification* of aldehydes.

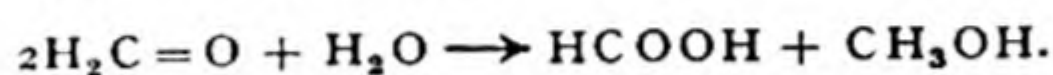
Aldehyde resin must be considered as a product of a further reaction between

molecules of aldol by which water is split off; aldol itself easily loses a molecule of water on warming and is converted into crotonaldehyde:



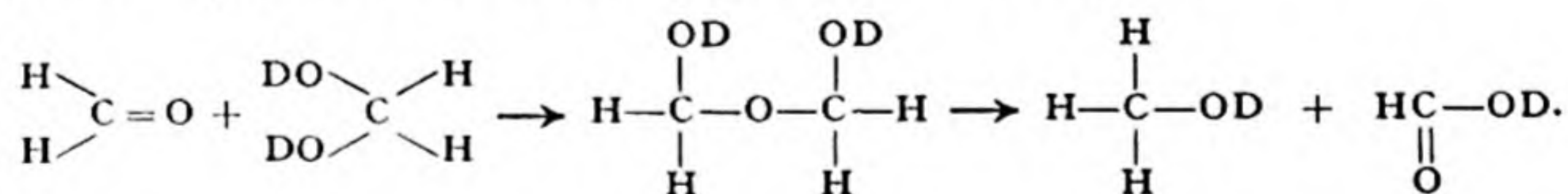
7. Aldehydes can react in the presence of strong bases in still another way, such that part of the aldehyde is oxidised to the corresponding acid and part is reduced to the corresponding alcohol. This reaction, called the CANNIZZARO reaction, is a characteristic of aromatic aldehydes; in the aliphatic series methanal (formaldehyde) can undergo this reaction.

The CANNIZZARO reaction may be regarded as a reaction between two molecules of methanal and one molecule of water:



The obvious assumption that a hydrogen atom from the molecule of water takes part in the formation of the methyl group in the methanol is incorrect, as appears from an *investigation* carried out *with the help of heavy water* (D_2O) (FREDENHAGEN and BONHOEFFER). Pure paraform was treated with a 20 % solution of potassium hydroxide in heavy water. The methanol formed was separated in a pure state and then burnt over copper oxide. The water produced in the combustion was examined for its deuterium oxide content, by a very accurate determination of the specific gravity or of the vapour pressure. From this the deuterium content of the methanol formed in the CANNIZZARO reaction was calculated, and it agreed with one atom of deuterium per molecule of methanol.

In this connection the following must be taken into consideration. It has been found, that compounds containing a hydroxyl group rapidly exchange the hydrogen atom of this group for an atom of deuterium when brought into contact with heavy water. On this account, the methanol produced in the above experiment will contain the group $-\text{OD}$. Since only one atom of deuterium is found per molecule of methanol, the CH_3 -group contains only light hydrogen. It is assumed that the CANNIZZARO reaction with methanal in heavy water takes place as follows: a molecule of methanal reacts with the "hydrate" of a second molecule of methanal with the formation of a compound having the structure of a "semi-acetal", then migration of a hydrogen atom and the rupture of the ether-oxygen bond takes place:

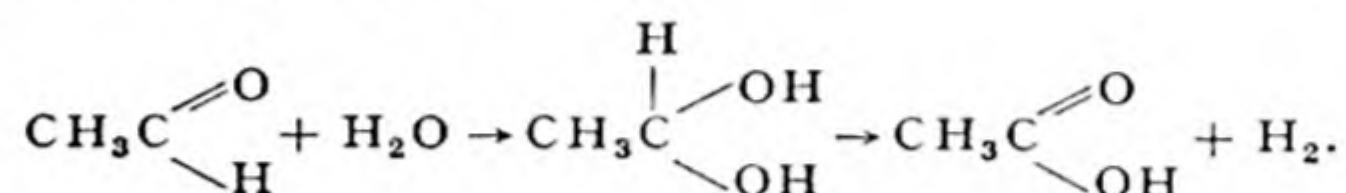


It is assumed that the reaction takes the same course in light water. The CANNIZZARO reaction with benzaldehyde takes the same course, as was shown in a similar manner.

8. *Reactions on aldehydes.* For the detection of aldehydes use is made of:
a. resinification by alkalis; *b.* the reducing action of aldehydes on ammoniacal silver solution. The latter is obtained by adding a slight excess of potassium hydroxide to a solution of silver nitrate and then adding sufficient ammonia

to dissolve the precipitate of silver hydroxide by forming complex compounds. A dilute aqueous solution of an aldehyde precipitates metallic silver from this reagent (silver mirror). This reaction is also brought about by some other reducing agents, however. *c.* A solution of fuchsin decolourised with sulphur dioxide is coloured reddish violet on the addition of an aldehyde by the formation of coloured condensation products.

The conversion of aldehyde into acids can also occur in the absence of oxygen. WIELAND shook a solution of acetaldehyde in water with palladium black with the exclusion of air. In this experiment acetic acid was produced, while the palladium took up hydrogen. It is assumed that a hydrate of the aldehyde is first formed from which hydrogen is subsequently split off:



If access to air is possible (or if an oxidising agent is added) the hydrogen attached to the palladium is oxidised to water and the formation of more acetic acid occurs; the palladium then acts as a catalyst. WIELAND also showed that anhydrous acetaldehyde is not oxidised with dry silver oxide; on adding water the reaction takes place immediately.

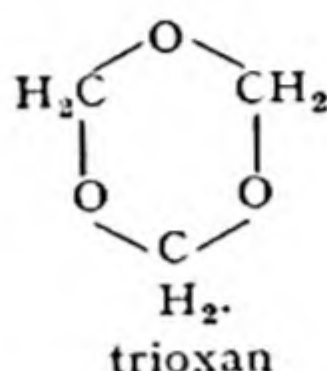
62. *Methanal* or *formaldehyde*, CH_2O , was first prepared by A. W. HOFMANN (1868) by passing methanol vapour and air over heated platinum; in the *technical preparation* of formaldehyde copper gauze is used as the contact substance. Formaldehyde is also formed by irradiating a mixture of carbon monoxide and hydrogen with ultra-violet light, as well as by the action of ozone on methane or ethylene. It is produced in small quantities by incomplete combustion of methane (24) and many organic substances such as wood, peat, etc. Methanal polymerises very easily. Gaseous monomeric methanal can be obtained by heating paraform; it is a colourless, combustible gas with a penetrating odour, which vigorously attacks the mucous membranes. Liquid formaldehyde begins to polymerise at as low a temperature as -80° . It is readily soluble in water but in this solution only a small proportion is present in the uncombined state.

The ultra-violet spectrum of a dilute aqueous solution of formaldehyde does not show the characteristic bands of $\text{O}=\text{CH}_2$, which are observed in a dilute solution of the substance in hexane. Therefore, it is assumed that methanal is present in aqueous solution mainly in the form of the hydrate $\text{CH}_2(\text{OH})_2$. Examination of the Raman spectrum leads to the same conclusion. Similar observations have been made for acetaldehyde in aqueous solution. The hydrates of unsubstituted aldehydes are unstable and cannot be isolated as such (compare, however, chloral hydrate 128). The acetals (60) may be regarded as the ethers of the hypothetical 1,1-dihydroxyalkanes, $\text{RCH}(\text{OH})_2$. A concentrated aqueous solution of formaldehyde contains poly-oxy-methylene glycols, which are produced from the hydrated form of formaldehyde: $\text{HOCH}_2\text{OH} + [\text{HOCH}_2\text{OH}]_x + \text{HOCH}_2\text{OH} \rightarrow \text{HOCH}_2\text{O}-[\text{CH}_2\text{O}]_x-\text{CH}_2\text{OH}$ or $\text{HO}[\text{CH}_2\text{O}]_{x+2}\text{H}$

These compounds exist in equilibrium with the hydrated form of methanal so that a solution of formaldehyde in water behaves in most chemical reactions as if the formaldehyde is present in the free state.

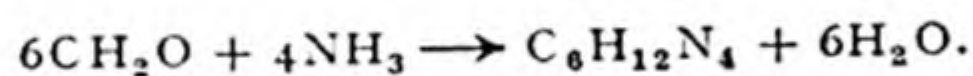
STAUDINGER has actually isolated some of these polyoxymethylene glycols; on warming they split up into formaldehyde and water.

Moreover, several polymers of methanal having the composition $(\text{CH}_2\text{O})_n$ are also known. Trioxan, $(\text{CH}_2\text{O})_3$ is crystalline, melts at 61° and boils at 115° ; it has no reducing properties and is split up into methanal by warming with mineral acids. A cyclic structure:

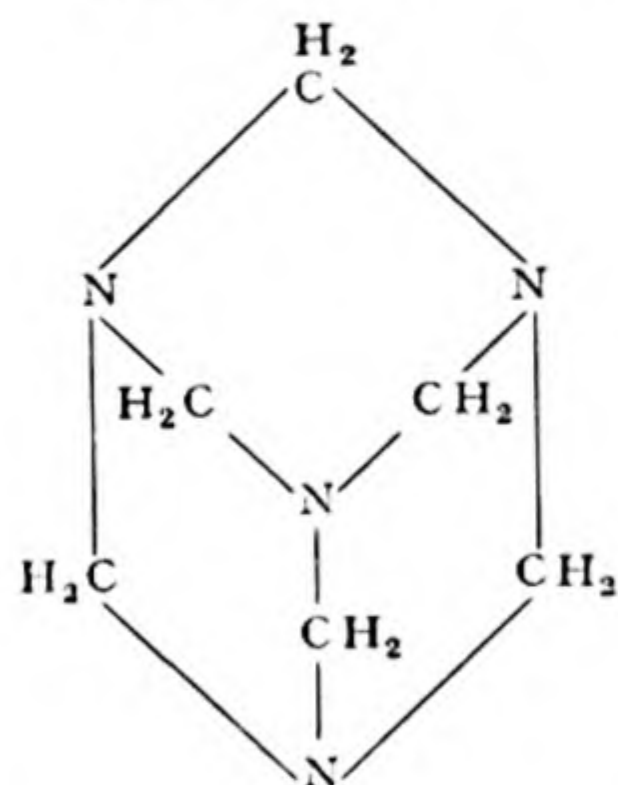


is given to this compound (compare paraldehyde).

In some respects methanal has different properties from the succeeding members of the homologous series. By the action of concentrated ammonia on a concentrated solution of formaldehyde in water, a crystalline compound $(\text{CH}_2)_6\text{N}_4$, *hexamethylene-tetramine* or *hexamine* is formed:

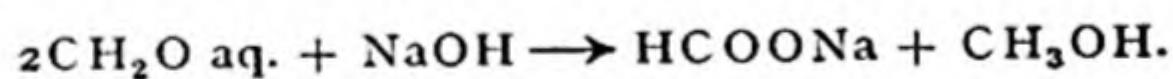


Chiefly on the basis of X-ray examination, the structure given here is usually attributed to this compound.



Hexamethylenetetramine, an old and incorrect name, has weakly basic properties. It is used in the manufacture of synthetic resins and in medicine as an internal disinfectant (urotropine).

Under the influence of strong alkali formaldehyde undergoes the CANNIZZARO reaction (61) with the formation of sodium formate (69) and methanol:



Methanal undergoes the aldol condensation under the influence of weak bases (see 61) with the formation of monosaccharides $(\text{CH}_2\text{O})_6$ (159).

For practical use formaldehyde is put out as *formalin* or *formal*, i.e. the commercial name for a solution of about 40 % formaldehyde in water, or as *paraformaldehyde* (*paraform*). This latter substance is obtained by evaporating an aqueous solution of formaldehyde and consists of a mixture of polyoxymethylene glycols, $\text{HO}(\text{CH}_2\text{O})_n\text{H}$; in current brands the average value of "n" is about 50. Paraform is a colourless solid, which splits up into methanal and a little water vapour on warming. Formaldehyde is used in dilute aqueous solution and also in the gaseous form as a disinfectant.

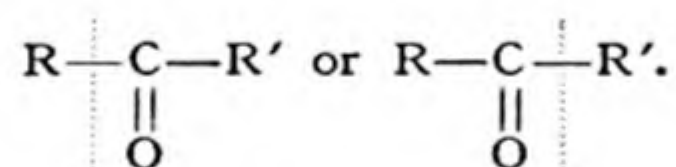
Formaldehyde gives condensation products with phenols, which are used as synthetic resins and plastic products. Synthetic resins are also obtained from formaldehyde and casein. A solution of formaldehyde acts on proteins and converts them into solid, elastic products (preservation of anatomical specimens with formol). Formaldehyde is also used in the preparation of various synthetic dyestuffs and in the leather industry.

63. *Ethanal, acetaldehyde*, $\text{CH}_3\text{C}\begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{H} \end{smallmatrix}$, was first prepared in a pure state by LIEBIG (1835); it is a light, mobile liquid with a not unpleasant and somewhat stupefying odour. It is miscible with water in all proportions, very volatile and easily oxidisable. Ethanal is prepared from acetylene (91) on a large scale as an intermediate for the synthesis of acetic acid (70).

Higher aldehydes. *Octanal* or *caprylaldehyde*, $\text{C}_7\text{H}_{15}\text{CHO}$ and *nonanal* or *pelargonaldehyde*, $\text{C}_8\text{H}_{17}\text{CHO}$, occur in essential oils (e.g. in rose oil and in lemon oil) and are used as perfumes.

ALKANONES (KETONES)

64. In the discussion of the structure of the alkanones it has already been mentioned that these compounds are split up by vigorous oxidation with chromic acid or with potassium permanganate, the carbon chain being broken at the carbonyl group (see 57). The rupture of the carbon chain can occur in either of two places:



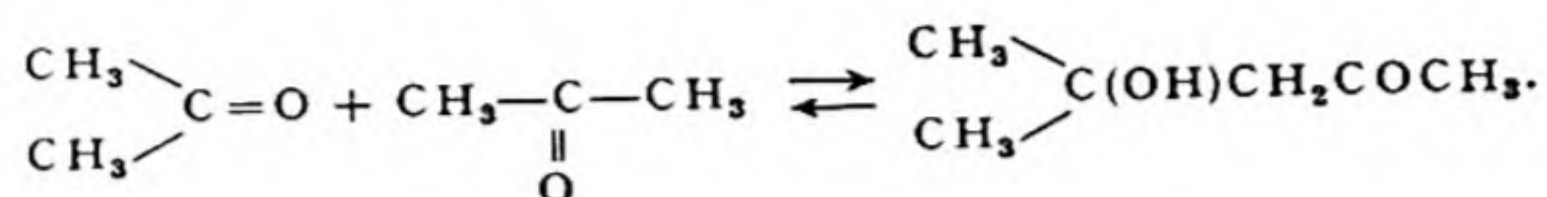
From undecanone-2 (methyl nonyl ketone) $\text{CH}_3 - \text{C} - \text{C}_9\text{H}_{19}$ there should be

produced: formic acid, HCOOH , and nonane 1-carboxylic acid, $\text{C}_9\text{H}_{19}\text{COOH}$, by fission occurring at I, or acetic acid, CH_3COOH , and octane 1-carboxylic acid, $\text{C}_8\text{H}_{17}\text{COOH}$, by fission occurring at II. Experience has shown that oxidation takes place in both directions, so that in general, four acids can be produced from a ketone; usually that mode of fission predominates in which the carbonyl group remains attached to the smaller alkyl residue.

Ketones are much less readily oxidised than aldehydes; they do *not* react therefore with ammoniacal silver solution. The alkanones do not form addition products with ammonia like the aldehydes. Compounds like *diacetoneamine*, $\text{C}_6\text{H}_{13}\text{ON}$ ($= 2\text{C}_3\text{H}_6\text{O} + \text{NH}_3 - \text{H}_2\text{O}$) and *triacetoneamine*, $\text{C}_9\text{H}_{17}\text{ON}$, ($= 3\text{C}_3\text{H}_6\text{O} + \text{NH}_3 - 2\text{H}_2\text{O}$), can be formed from acetone and ammonia but these are produced by the elimination of water.

Ketones do *not* polymerise. By the action of barium hydroxide on acetone

a condensation product, *diacetone alcohol* or *4-hydroxy-4-methylpentanone-2*, a substance, which contains a ketone group and an alcohol group, is produced:



This reaction may be compared with the aldol condensation with aldehydes.

The boiling points and melting points of a few alkanones are given in Table 18.

TABLE 18
MELTING AND BOILING POINTS OF SOME ALKANONES

Name	Formula	M.p.	B.p.
Propanone, acetone	$(\text{CH}_3)_2\text{CO}$	-94.8°	56.2°
Butanone, methyl ethyl ketone	$\text{CH}_3\text{COC}_2\text{H}_5$	-86.4°	79.6°
Pentanone-3, diethyl ketone	$\text{C}_2\text{H}_5\text{COC}_2\text{H}_5$	-39.9°	102.0°
Hexanone-2, methyl butyl ketone	$\text{CH}_3\text{COC}_4\text{H}_9$	-56.9°	127°

65. *Propanone, acetone* $(\text{CH}_3)_2\text{CO}$. Acetone is prepared on a commercial scale:

1. by heating calcium acetate, 2. by passing acetic acid vapour at about 480° over catalytically active metallic oxides (alumina, lime + magnesium oxide) and 3. by decomposing starch by means of certain bacteria (*bacillus aceto-aethylicus* and *bacillus macerans*), when ethyl alcohol is produced besides acetone.

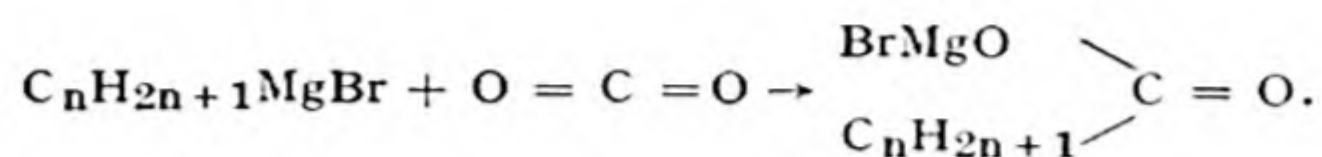
Acetone is a colourless liquid, with a specific gravity of 0.812 at 0° , and a characteristic burnt smell. It is miscible with water in all proportions and is a good solvent for many organic substances; it is used in the manufacture of smokeless gunpowder and celluloid and is the starting point for the manufacture of important compounds, e.g. chloroform and iodoform.

Normal urine contains very small quantities of acetone, which are greater however in certain pathological conditions (*diabetes mellitus*).

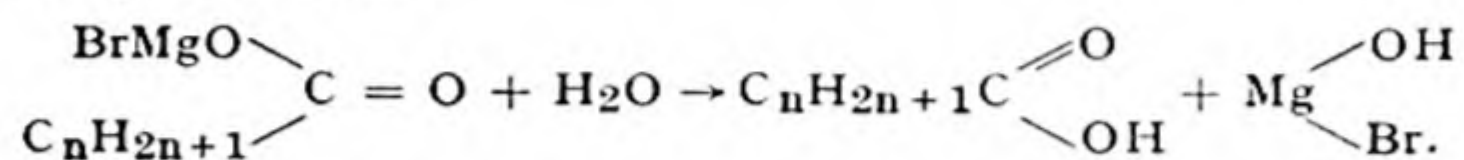
(viii) MONOBASIC ALKANE CARBOXYLIC ACIDS $\text{C}_n\text{H}_{2n}\text{O}_2$

66. There are various methods for the formation of the monobasic acids of the general formula $\text{C}_n\text{H}_{2n}\text{O}_2$ from which the structure of these compounds can be deduced. When dry carbon dioxide is passed into an ethereal solution of alkylmagnesium bromide, a solid substance of the composition $\text{C}_n\text{H}_{2n+1}\text{MgBrCO}_2$ is precipitated. The alkyl-magnesium bromide enters into reaction

with the carbon dioxide, one of the double bonds between carbon and oxygen being transformed into a single bond; the alkyl group of the alkyl-magnesium bromide becomes attached to carbon while the magnesium atom combines with the oxygen atom because magnesium has a greater affinity for oxygen:

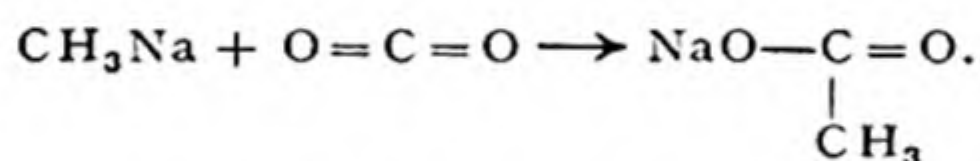


When this addition product is treated with water, an acid and basic magnesium bromide are produced:

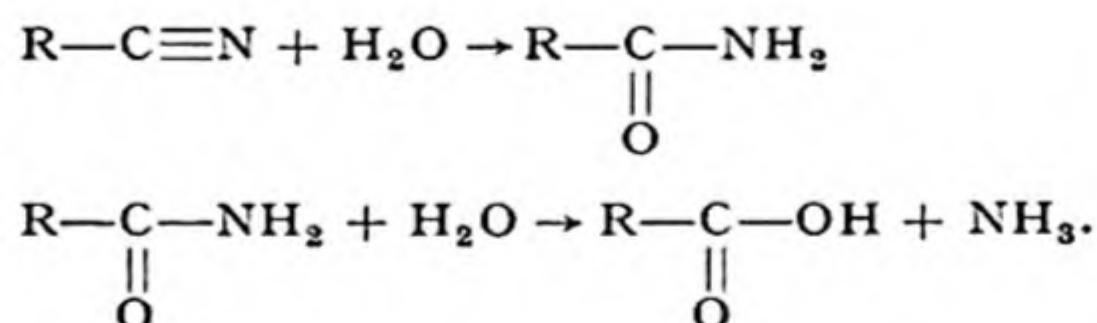


According to this method of formation, a group $\text{—C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$, called the *carboxyl group*, attached to an alkyl group, occurs in the acids of formula $\text{C}_n\text{H}_{2n}\text{O}_2$.

Another synthesis, similar to the one above, but which is applicable in a few cases only, confirms this opinion. This is the formation of the sodium salt of acetic acid, for example, by the action of dry carbon dioxide on sodium methyl:

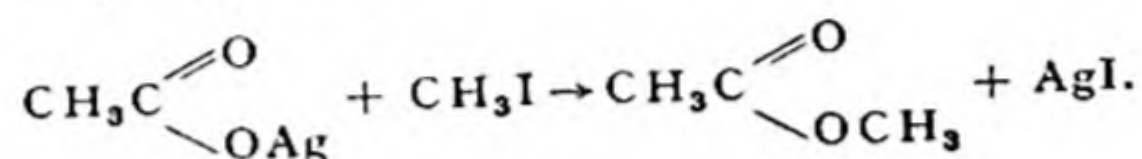


The formation of acids by the hydrolysis of carbonitriles amounts to the addition of water; because an acid with the same number of carbon atoms is produced from the carbonitrile, this addition can take place only on the $\text{—C}\equiv\text{N}$ group. We shall see later, that in the conversion of carbonitriles into acids, an intermediate product, an acid amide R—CO—NH_2 , which is produced by the addition of one molecule of water to the CN-group, may be formed. This acid amide is split by a second molecule of water in the subsequent stage of the reaction:



This method of formation also is in agreement with the structure derived above. The generic name for compounds, containing the group $\text{—C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$, is *carboxylic acids*. The action of phosphorus chlorides shows that this group contains a hydroxyl group. As with the alcohols, OH is then replaced by Cl.

The acids $C_nH_{2n}O_2$ are monobasic, therefore, one hydrogen atom can be replaced by metals with the formation of salts. It is an obvious assumption that this is the hydrogen atom in the carboxyl group because this is the only hydrogen atom in the molecule, which is combined in a particular way, namely to oxygen. This assumption is supported also by the following fact. When methyl iodide is allowed to react with the silver salt of acetic acid, $C_2H_3O_2Ag$, for example, a substance $C_2H_3O_2CH_3$ is produced, which no longer possesses acid properties:



The carboxylic acids are produced by oxidation of primary alcohols (29) the grouping $-CH_2OH$ being converted into $-C \begin{array}{l} \nearrow O \\ \searrow OH \end{array}$. When this occurs it is seen that by replacing the two hydrogen atoms by a doubly bound oxygen atom, the properties of the hydroxyl group in $-C \begin{array}{l} \nearrow O \\ \searrow OH \end{array}$ are altered when compared with the properties of the hydroxyl group in $-CH_2OH$; in the former grouping the hydrogen atom is ionisable and in the latter it is not. Other methods of forming these acids are given in 123 and 148.

67. Nomenclature. Acids of the general formula $C_nH_{2n+1}COOH$ are called alkane carboxylic acids, because these substances are regarded as derivatives of hydrocarbons in which one hydrogen atom is replaced by the carboxyl group; CH_3COOH methane carboxylic acid (acetic acid), C_2H_5COOH ethane carboxylic acid (propionic acid), C_3H_7COOH propane carboxylic acid (butyric acid). This nomenclature is not applicable to the first member of the series, formic acid. Because a number of acids of this series are obtained as fission products from fats, the alkane carboxylic acids are also called *fatty acids*.

The group of atoms $C_nH_{2n+1}C=O$, which remains when the hydroxyl group is removed from an alkane carboxylic acid, is named after the acid from which it is derived by adding the suffix "yl"; thus HCO *hydrogen-carbonyl* (a hypothetical name, which is never used in practice) or *formyl* (from *acidum formicum*), CH_3CO *methane-carbonyl* or *acetyl* (from *acidum aceticum*), C_2H_5CO *ethane-carbonyl* or *propionyl*, C_3H_7CO *propane-carbonyl* or *butyryl* (from *acidum butyricum*), etc.

Some of the *physical properties of the alkane carboxylic acids* are given in Table 19. While the boiling points increase regularly with the number of carbon atoms in the molecule, the melting points of the acids with even numbers of carbon atoms are higher than those of the preceding and

TABLE 19
SOME PHYSICAL CONSTANTS OF ALKANE CARBOXYLIC ACIDS

Name		Formula	M.p.	B.p.	Spec. grav. d ₄ ²⁰
	Formic acid	CH ₂ O ₂	8.5°	100.8°	1.2203
Methane carboxylic acid	Acetic acid	C ₂ H ₄ O ₂	16.67°	118.1°	1.0492
Ethane carboxylic acid	Propionic acid	C ₃ H ₆ O ₂	—20.8°	141.3°	0.9930
Propane 1-carboxylic acid	Butyric acid	C ₄ H ₈ O ₂	— 5.50°	164.0°	0.9577
Butane 1-carboxylic acid	Valeric acid	C ₅ H ₁₀ O ₂	—34.5°	186.3°	0.9392
Pentane 1-carboxylic acid	Caproic acid	C ₆ H ₁₂ O ₂	— 3.9°	202°	0.9270
Hexane 1-carboxylic acid	Heptanoic acid	C ₇ H ₁₄ O ₂	— 7.5°	223°	0.9181
Heptane 1-carboxylic acid	Caprylic or octoic acid	C ₈ H ₁₆ O ₂	16.5°	239°	0.9088
Octane 1-carboxylic acid	Nonoic or pelar- gonic acid	C ₉ H ₁₈ O ₂	12.5°	254°	0.9057
Nonane 1-carboxylic acid	Capric or decoic acid	C ₁₀ H ₂₀ O ₂	31°	268°	0.8858d ₄ ²⁰
Decane 1-carboxylic acid	Undecoic acid	C ₁₁ H ₂₂ O ₂	30°	164° 15 mm.	—
Undecane 1-carboxylic acid	Lauric acid	C ₁₂ H ₂₄ O ₂	44°	180° 16 mm.	0.8573d ₄ ²⁰
Dodecane 1-carboxylic acid	Tridecoic acid	C ₁₃ H ₂₆ O ₂	45.5°	200° 24 mm.	
Tridecane 1-carboxylic acid	Myristic acid	C ₁₄ H ₂₈ O ₂	53.6°	199° 16 mm.	0.8528d ₄ ²⁰
Tetradecane 1-carboxylic acid	Pentadecoic acid	C ₁₅ H ₃₀ O ₂	54°	257° 100 mm.	
Pentadecane 1-carboxylic acid	Palmitic acid	C ₁₆ H ₃₂ O ₂	62.62°	271.5° 100 mm.	0.8487d ₄ ²⁰
Hexadecane 1-carboxylic acid	Margaric acid	C ₁₇ H ₃₄ O ₂	60.5°	227° 100 mm.	
Heptadecane 1-carboxylic acid	Stearic acid	C ₁₈ H ₃₆ O ₂	69.6°	291° 100 mm.	0.8390d ₄ ²⁰

succeeding acids with odd numbers, see graph, Fig. 21, p. 116. This phenomenon is observed also in some other homologous series.

The first nine members of this series are liquids, the first three having a strongly acrid smell. The members with ten and more carbon atoms are solid at ordinary temperatures and are odourless; the solubility in water decreases as the number of carbon atoms increases and is very low for the higher members. The higher members are only very slightly volatile and cannot be distilled under ordinary pressure without decomposition.

On association in lower fatty acids see 41.

68. *Electrolytic dissociation.* It has been found that the dilution law of OSTWALD $\frac{\alpha^2}{(1-\alpha)\nu} = k$, where the "dilution" ν = the number of litres of

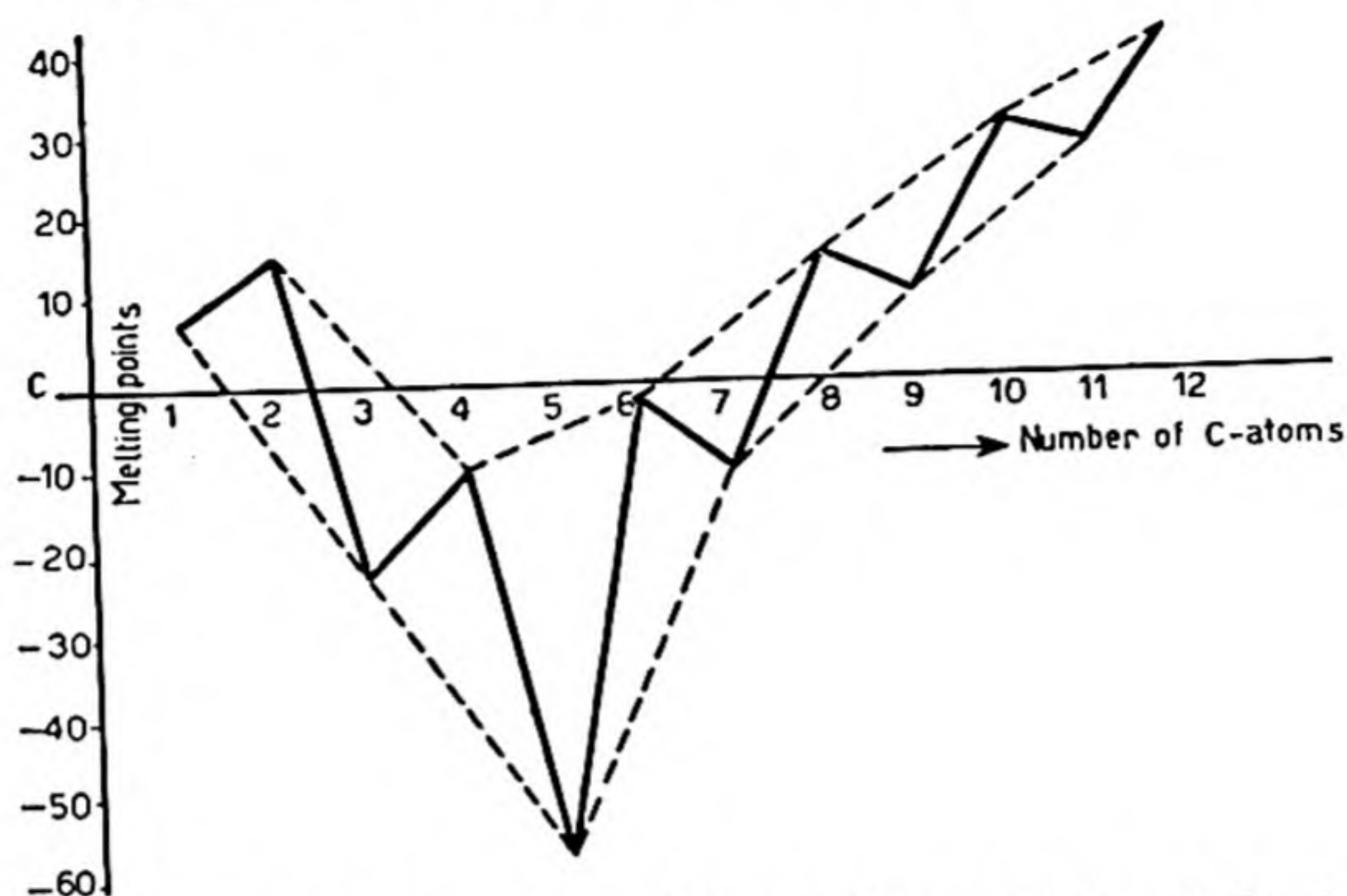


Fig. 21. Graphical representation of the melting points of the fatty acids

solution per grammolecule of dissolved substance, accurately represents the relationship between the degree of ionisation and the dilution for weak electrolytes, particularly for very many organic acids, so that the same value is found for k , within limits of the experimental error, at different dilutions. Table 20 gives some examples of this.

TABLE 20

ELECTROLYTIC DISSOCIATION OF SOME ALKANE CARBOXYLIC ACIDS

Acetic acid			Propionic acid			<i>n</i> -Butyric acid		
v	100α	k	v	100α	k	v	100α	k
8	1.193	0.0000180	8	1.016	0.0000130	8	1.068	0.0000144
16	1.673	0.0000179	16	1.452	0.0000134	16	1.536	0.0000150
32	2.380	0.0000182	32	2.050	0.0000134	32	2.165	0.0000149
64	3.33	0.0000179	64	2.895	0.0000135	64	3.053	0.0000150
128	4.68	0.0000179	128	4.04	0.0000133	128	4.292	0.0000150
1024	12.66	0.0000177	1024	10.79	0.0000128	1024	11.41	0.0000144

The strength of an acid is determined by the degree to which it is dissociated in aqueous solution. Since, according to OSTWALD'S formula, the ionisation constant k increases with the degree of ionisation, the numerical value of k is a measure of the strength of the acid. The values of k for some alkane carboxylic acids are given in Table 21.

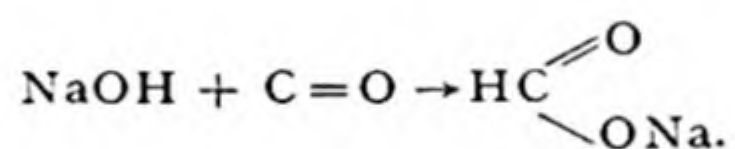
It is seen that formic acid is much stronger than the succeeding acids of the series, which themselves do not differ appreciably in strength. Most organic acids are very much weaker than hydrochloric acid, nitric acid or

sulphuric acid. Thus in a normal solution, hydrochloric acid is already split up into ions to an extent of 80 %, but acetic acid, on the other hand, to an extent of only 1.2 % in a 1/8th normal solution.

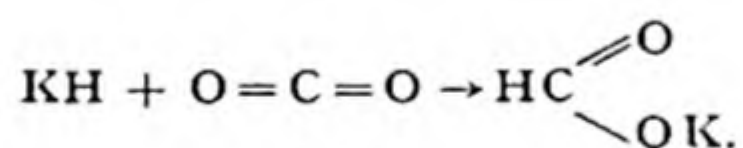
TABLE 21
IONISATION CONSTANTS OF SOME ALKANE CARBOXYLIC ACIDS

Name	<i>k</i>
Formic acid	0.000205
Acetic acid	0.000018
Propionic acid	0.000013
<i>n</i> -Butyric acid	0.000014
<i>n</i> -Valeric acid	0.000016

69. *Formic acid*. This compound occurs in the bodies of red ants (*formica rufa*) from which the name *formic acid* or *acidum formicum* is derived. Various plants, *e.g.* stinging nettles, also contain formic acid. The sodium salt of formic acid, *sodium formate*, is prepared on a commercial scale by the action of carbon monoxide on sodium hydroxide at about 150° and at high pressures:



This method of formation was discovered by BERTHELOT. The formation of potassium formate by the action of carbon dioxide on potassium hydride is of interest:



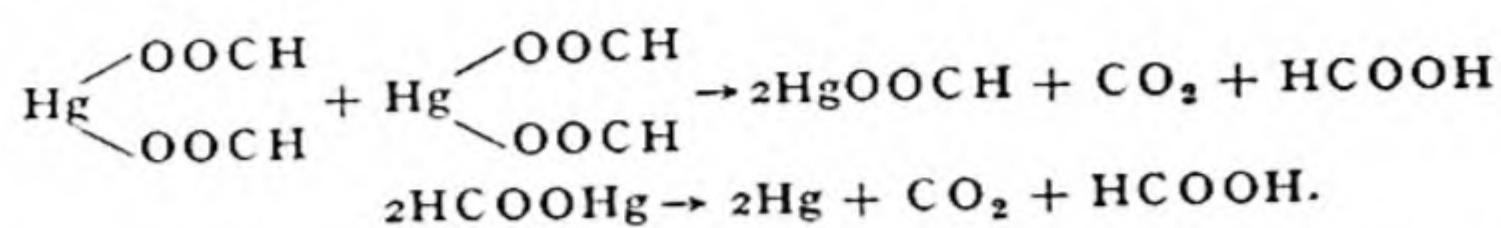
Analogous to this reaction, in which carbon dioxide is converted into a salt of formic acid by reduction, is the preparation of potassium formate by the action of hydrogen at 70° and 60 atm. pressure on a solution of potassium bicarbonate in presence of palladium black as catalyst.

Anhydrous formic acid is a colourless, mobile liquid with a very pungent smell; it attacks the skin.

The chemical behaviour of formic acid deviates in several respects from that of subsequent members of the series; it has already been mentioned that formic acid is considerably stronger than its homologues. Formic acid is easily oxidised and therefore has reducing properties. Chromic oxide reacts violently with anhydrous formic acid producing carbon dioxide and water. A solution of sodium formate is oxidised by potassium permanganate.

When mercuric oxide is dissolved in formic acid, mercuric formate is first produced; on warming the solution, this salt decomposes into formic acid,

carbon dioxide and mercurous formate, which separates as a white precipitate. On warming for a longer time metallic mercury separates:



Thus in this reaction half of the formic acid combined in the mercuric formate is oxidised. A similar reaction takes place when a solution of silver formate is warmed and metallic silver separates; thus formic acid reduces a solution of silver nitrate.

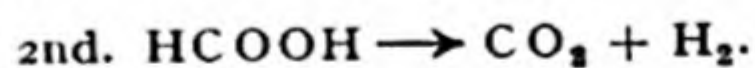
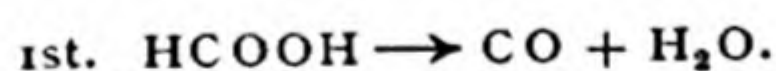
In its behaviour towards oxidising agents formic acid differs sharply from its homologues which are much more stable towards these reagents. When the structural formula of formic acid is compared with that of its homologues:



it is seen, that when the C-atom of the carboxyl group is oxidised further, this can happen in formic acid only by a H—C bond being broken, but with the homologues a C—C bond must be ruptured.

The difference in behaviour towards oxidising agents between formic acid and succeeding members of the series, indicates that in these reactions the bond between a hydrogen atom and the C-atom of the carboxyl group is more easily broken than the bond between a carbon atom of an alkyl group and the C-atom of the carboxyl group. A similar case arises in the difference in oxidisability between aldehydes and ketones (57).

Another property of formic acid, which is not encountered with the homologues, is the decomposition with concentrated sulphuric acid whereby carbon monoxide and water are produced. Formic acid may also decompose in another way, namely, into carbon dioxide and hydrogen:



Both reactions can take place when the vapour of formic acid is passed over certain catalysts at a temperature round about 300° ; in presence of finely divided copper or nickel, zinc oxide or stannous oxide (SnO), the 2nd decomposition occurs; with aluminium oxide or silicon dioxide as contact material the reaction takes place according to the 1st scheme. This is an excellent example of the influence of the nature of the catalyst on the course of a chemical reaction.

The decomposition of formic acid can also be accomplished by ultra-violet light; it then depends on the wave-length of the light as to which of the two reactions 1 and 2 predominates.

70. *Acetic acid, Methane carboxylic acid* CH_3COOH . Dilute acetic acid was known in ancient times in the form of wine vinegar. Many species of plants contain esters of acetic acid and the substance itself occurs in the free state in the vegetable kingdom.

Acetic acid is prepared commercially in three ways:

1. The oldest method depends on the oxidation of dilute alcohol by atmospheric oxygen under the influence of bacteria (*mycoderma aceti*). Vinegar is obtained in this way from wine or beer. In the *quick vinegar process*, dilute alcohol (5 — 10 %) with beer or an extract of malt, which must serve as food for the bacteria, is allowed to drip over beech shavings; air is forced in at the bottom of the vat so that it comes into intimate contact with the descending liquid. The conditions must be so chosen that the acetic acid bacteria, which bring about the oxidation, can develop prolifically, *e.g.* by keeping the contents at the most suitable temperature (between 25° and 35°).

2. It has already been mentioned in 30 that acetic acid is also produced in the dry distillation of wood (wood vinegar). The acetic acid is converted into calcium acetate by the addition of slaked lime; after separation and purification, the calcium acetate is decomposed with sulphuric acid and the acetic acid recovered by distillation.

3. Large quantities of acetic acid are at present produced synthetically starting from acetylene (see 91).

Pure acetic acid solidifies at 16.67° and the solid closely resembles ice in appearance; the name *glacial acetic acid* for anhydrous material is derived in this way. This substance has a very pungent odour and causes burns on the skin. On mixing acetic acid with water, heat is developed and the volume contracts.

Most salts of acetic acid, *methane carboxylates* or *acetates*, are soluble in water; the silver salt is difficultly soluble. When ferric chloride is added to a solution of an acetate, a red colouration is produced due to the formation of ferric acetate (the same colour is also produced, however, by salts of formic acid and propionic acid). When the solution is boiled, provided the dilution is sufficient, a brownish red precipitate of a complex ferriacetato-compound is formed and acetic acid is liberated.

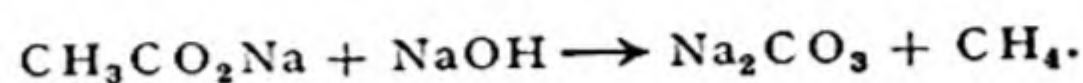
Acetic acid and its esters are used both in the laboratory and commercially for a large number of syntheses and preparations.

Lead acetate (*sugar of lead*) and basic lead acetates (*lead vinegar*) are used for the

manufacture of white lead (basic lead carbonate). Aluminium acetate and chromium acetate are soluble in water, but are converted into basic salts when the aqueous solutions are heated; on this depends the use of aluminium and chromium acetates as mordants in the dyeing of woven fabrics.

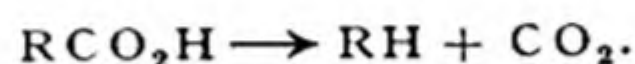
As regards the chemical properties of acetic acid, mention has already been made of the stability of this substance towards oxidising agents; oxidations with chromic oxide, for example, can be carried out in glacial acetic acid as solvent.

On heating a mixture of anhydrous sodium acetate and soda-lime, methane (16) is formed:

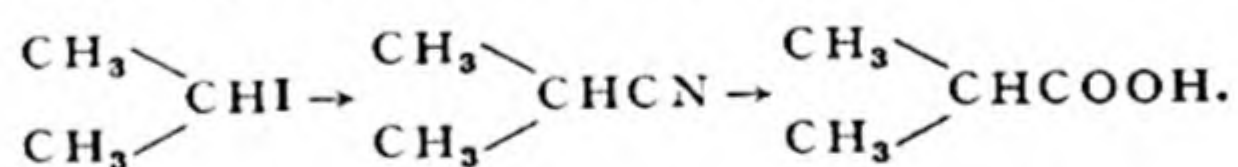
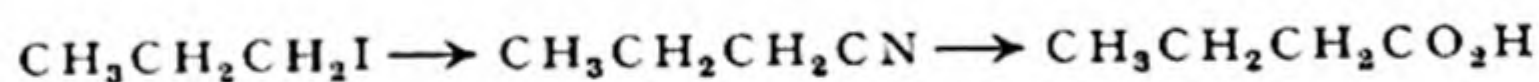


In principle the same reaction can be carried out with the sodium salts of homologues of acetic acid; *e.g.* propane can be prepared from sodium butyrate. This method is not suitable however as a method of preparation for the higher alkanes, since the hydrocarbons formed, decompose at the temperature necessary for the reaction.

Acetic acid and its homologues are split up by ultra-violet light, mainly in accordance with the equation:



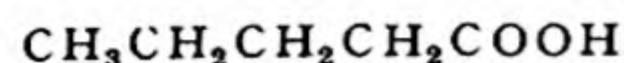
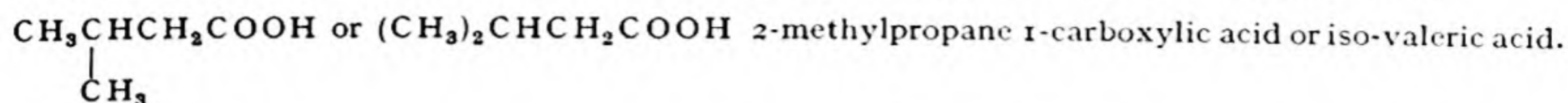
71. Propane carboxylic acids, Butyric acids $\text{C}_4\text{H}_8\text{O}_2$. Two isomeric acids $\text{C}_4\text{H}_8\text{O}_2$ are known; *propane 1-carboxylic acid* or *normal butyric acid*, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ and *propane 2-carboxylic acid* or *isobutyric acid*, $(\text{CH}_3)_2\text{CHCO}_2\text{H}$. The structures of these acids follows from their synthesis; the normal acid is produced from *n*-propyl iodide the iso-compound from isopropyl iodide:



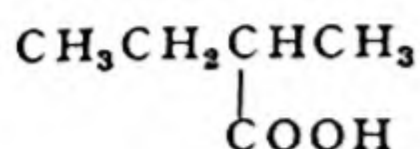
Normal butyric acid has this name because it can be obtained from butter; it is also called fermentation butyric acid since it may be produced by fermentation of sugar or starch by *bacillus butyricus*; this is the way it is prepared technically. It has a most unpleasant odour.

The calcium salts of the isomeric butyric acids show a remarkable difference, the salt of the normal acid is *more difficultly soluble in hot water* than in cold; the calcium salt of the iso-acid on the other hand, follows the general rule and is *more easily soluble in hot water* than in cold. According to the principle of mobile equilibrium, normal calcium butyrate should dissolve in water with the evolution of heat and calcium isobutyrate with the absorption of heat; this is actually what is observed.

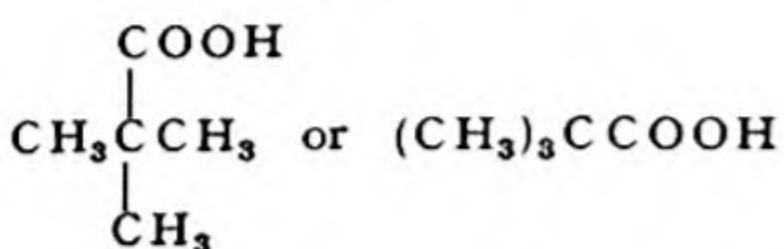
72. Butane carboxylic acids, Valeric acids $\text{C}_5\text{H}_{10}\text{O}_2$. According to the theory of structure four butane carboxylic acids are possible and all these are known.

butane 1-carboxylic acid or *n*-valeric acid.

2-methylpropane 1-carboxylic acid or iso-valeric acid.



butane 2-carboxylic acid or methylethylacetic acid.



2-methylpropane 2-carboxylic acid or trimethylacetic acid.

n-Valeric acid is produced by the oxidation of pentanol-1, isovaleric acid by oxidation of 3-methylbutanol-1. The other two acids can be made by synthetic methods which establish their structure. (see 123).

Isovaleric acid occurs in the free state in root stocks of *valeriana officinalis*; it is used for the preparation of certain drugs.

73. *Higher alkane carboxylic acids (fatty acids)* $\text{C}_n\text{H}_{2n}\text{O}_2$. The higher alkane carboxylic acids with normal carbon chains are to be regarded as building stones of important vegetable and animal substances. The fats indeed consist of esters of glycerol in which this trihydric alcohol is esterified with higher alkane carboxylic acids, chiefly *pentadecane 1-carboxylic acid* or *palmitic acid*, $\text{C}_{16}\text{H}_{32}\text{O}_2$, and *heptadecane 1-carboxylic acid* or *stearic acid*, $\text{C}_{18}\text{H}_{36}\text{O}_2$, along with unsaturated acids (see 101).

Besides the alkane carboxylic acids with 16 and 18 carbon atoms, a number of others are also found as fission products of fats, *e.g.*, *nonadecane carboxylic acid* or *arachidic acid*, $\text{C}_{20}\text{H}_{40}\text{O}_2$, *tridecane carboxylic acid* or *myristic acid*, $\text{C}_{14}\text{H}_{28}\text{O}_2$, *undecane carboxylic acid* or *lauric acid*, $\text{C}_{12}\text{H}_{24}\text{O}_2$, *nonane carboxylic acid* or *capric acid*, $\text{C}_{10}\text{H}_{20}\text{O}_2$, *heptane carboxylic acid* or *caprylic acid*, $\text{C}_8\text{H}_{16}\text{O}_2$, *pentane carboxylic acid* or *caproic acid*, $\text{C}_6\text{H}_{12}\text{O}_2$, *propane carboxylic acid* or *butyric acid*, $\text{C}_4\text{H}_8\text{O}_2$.

Many higher fatty acids occur in different kinds of waxes and in essential oils as esters of other alcohols.

The arrangement of molecules in thin layers and the dimensions of the molecules of the higher fatty acids

74. When a small quantity of fat, *e.g.* *triolein*, dissolved in benzene is placed on the surface of water and the benzene is allowed to evaporate, a very thin layer of oil will remain behind. The surface of this oil layer can be measured after it has been rendered visible by dusting it with powdered talc. From the weight of oil taken, it is possible to calculate the volume and also the thickness of the oil layer. It is then found that the thickness is of the same order of magnitude as the dimensions of a single oil molecule. Therefore it is assumed that such a layer is only one molecule thick. This opinion has been confirmed by other kinds of experiments.

From measurements of the surface tension at the interface between water and

liquids immiscible with water, HARKINS has come to the conclusion, that the molecules of a number of organic substances in such interfaces are orientated in a definite direction; *e.g.* in the case of water and octanol the alcohol molecules are orientated with the hydroxyl groups turned towards the water, while the carbon chains of the alcohol molecules point in the opposite direction.

A monomolecular layer of palmitic acid for example, on water, has to be represented in such a way that the carboxyl groups dip into the water and the carbon chains stick up at right angles to the surface of the water. This holds also for esters of higher fatty acids, the ester group being directed towards the water.

By means of a method discovered by LANGMUIR it is possible to determine experimentally the smallest possible surface, which a monomolecular layer can occupy; in this condition the molecules of the monomolecular layer lie as closely together as possible.

When the experiment is carried out with a known weight of palmitic acid, with the aid of AVOGADRO's number (6.06×10^{23}) the total number of molecules in the monomolecular layer can be calculated and hence the surface occupied by one molecule in this layer can be computed. In the third column of Table 22 is given the available surface per molecule expressed in units of 10^{-16} square centimeters.

This number is the same for fatty acids with 14 to 22 carbon atoms inclusive. These substances differ considerably in the total size of their molecules, but occupy the same surface per molecule in the monomolecular layer. This is quite understandable if the molecules in this layer are so arranged that the carboxyl group dips into the water and the carbon chains stick up at right angles to the surface of the water. The numbers in the third column then represent the section or width of the carbon chain.

TABLE 22
MOLECULAR DIMENSIONS OF THE HIGHER FATTY ACIDS

Name	Formula	Width of the molecule in $\text{cm} \times 10^{16}$	Length of the molecule in $\text{cm} \times 10^8$
Myristic acid	$\text{CH}_3(\text{CH}_2)_{12}\text{COOH}$	21	21.1
Tetradecane carboxylic acid	$\text{CH}_3(\text{CH}_2)_{13}\text{COOH}$	21	22.4
Palmitic acid	$\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$	21	—
Cetyl alcohol	$\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{OH}$	21	22.4
Stearic acid	$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$	21	26.2
Stearamide	$\text{CH}_3(\text{CH}_2)_{16}\text{CONH}_2$	21	26.1
Behenic acid	$\text{CH}_3(\text{CH}_2)_{20}\text{COOH}$	21	31.4
Ethyl palmitate	$\text{CH}_3(\text{CH}_2)_{14}\text{COOC}_2\text{H}_5$	21	26.1
Ethyl behenate	$\text{CH}_3(\text{CH}_2)_{20}\text{COOC}_2\text{H}_5$	21	34.0
Tripalmitin	$(\text{C}_{15}\text{H}_{31}\text{COO})_3\text{C}_3\text{H}_5$	63	
Glycol dipalmitate	$(\text{C}_{15}\text{H}_{31}\text{COO})_2\text{C}_2\text{H}_4$	42	

In the fourth column is given the approximate calculated values for the length of the molecule in Ångström units (10^{-8} cm).

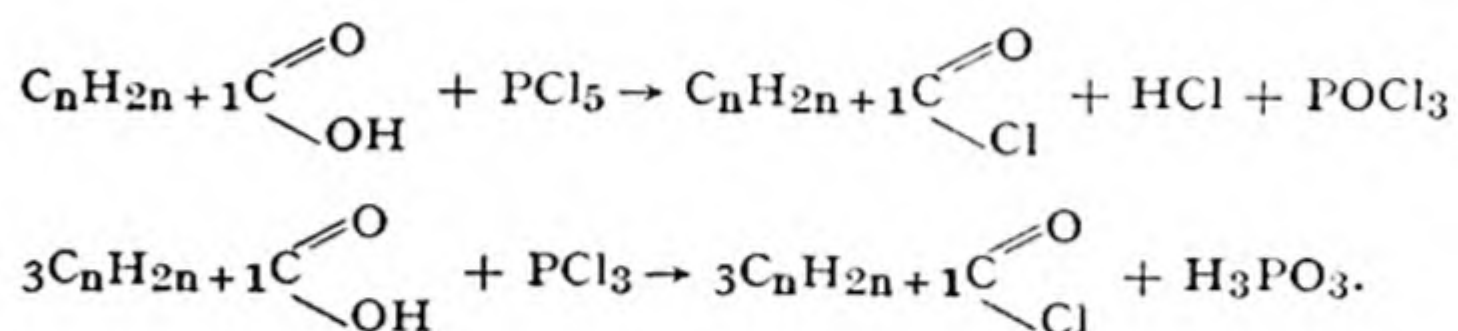
It follows that the molecules of these fatty acids have an elongated form. When the carbon chain is increased by one CH_2 group the length of the molecule increases by about 1.3 Ångström units (compare 37).

It may be seen also from the table, that in a monomolecular layer of *tripalmitin* on water, the width of a single molecule is not 21 but 63 Ångström units. This is to be expected, since the molecule of the fat dips into the water by the esterified carboxyl groups while the three carbon chains of the palmitic acid residues stand up above.

(ix) DERIVATIVES OF ALKANE CARBOXYLIC ACIDS PRODUCED BY
SUBSTITUTION IN THE CARBOXYL GROUP

(a) *Acid chlorides or alkane carbonyl chlorides*

75. These compounds are produced by the action of phosphorus pentachloride or phosphorus trichloride on alkane carboxylic acids:



From an acid of the general formula $\text{C}_n\text{H}_{2n}\text{O}_2$, there is produced an acid chloride of the general formula $\text{C}_n\text{H}_{2n-1}\text{OCl}$; an oxygen atom and a hydrogen atom are replaced by a monovalent chlorine atom; thus the OH-group of the carboxyl group must be substituted by a chlorine atom. The acid chlorides contain therefore the group $\text{—C}\begin{array}{l} \text{O} \\ \parallel \\ \text{Cl} \end{array}$.

These compounds are decomposed by water into the corresponding alkane carboxylic acid and hydrogen chloride; with the lower members, this reaction takes place very rapidly even at room temperatures.

The alkyl chlorides do *not* react with water at room temperatures.

A primary alkyl chloride has the structure $\text{R—C}\begin{array}{l} \text{H} \\ \diagup \\ \text{H} \\ \diagdown \\ \text{Cl} \end{array}$, an acid chloride has the structure $\text{R—C}\begin{array}{l} \text{O} \\ \parallel \\ \text{Cl} \end{array}$. Thus it follows that the bond between carbon and chlorine becomes less powerful when two hydrogen atoms also attached to the carbon atom are replaced by a doubly bound oxygen atom.

The lower members of the series of acid chlorides are liquids with a sharp, titillating odour, which fume in the air and may be distilled without decomposition. The chloride of formic acid is unknown but formyl fluoride $\text{HC}\begin{array}{l} \text{O} \\ \parallel \\ \text{F} \end{array}$ has been described. The boiling points of the acid chlorides are lower than those of the corresponding acids.

The acid chlorides react easily with alcohols with the formation of esters: (38, 77).

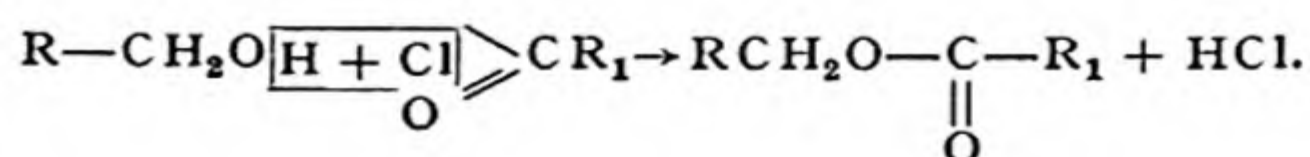
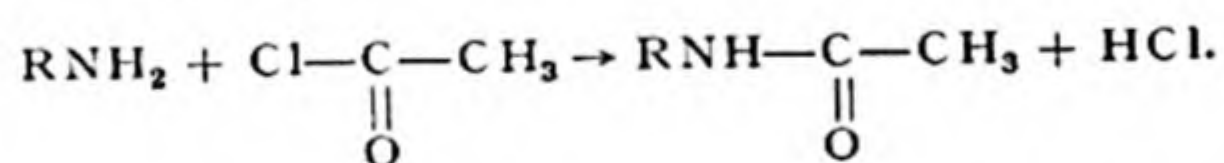


TABLE 23
BOILING AND MELTING POINTS OF SOME ACID CHLORIDES

Name	Formula	B.p.	M.p.
Acetyl chloride or methane carbonyl chloride	$\text{CH}_3\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{Cl} \end{array}$	51°	—
Propionyl chloride or ethane carbonyl chloride	$\text{C}_2\text{H}_5\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{Cl} \end{array}$	78°	—
Butyryl chloride or <i>n</i> -propane carbonyl chloride	$\text{C}_3\text{H}_7\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{Cl} \end{array}$	101°	—
Palmityl chloride or <i>n</i> -pentadecane carbonyl chloride	$\text{C}_{15}\text{H}_{31}\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{Cl} \end{array}$	192° (at 15 mm.)	12°
Stearyl chloride or <i>n</i> -heptadecane carbonyl chloride	$\text{C}_{17}\text{H}_{35}\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{Cl} \end{array}$	215° (at 15 mm.)	23°

Consequently, acid chlorides, especially *acetyl chloride*, are frequently used to find out whether one or more hydroxyl groups are present in an organic compound. An analysis of the product obtained, shows whether an acetyl compound has been produced and how many acetyl groups have been introduced. It is also possible to determine the quantity of acetic acid which is split off when the acetyl derivative is hydrolysed.

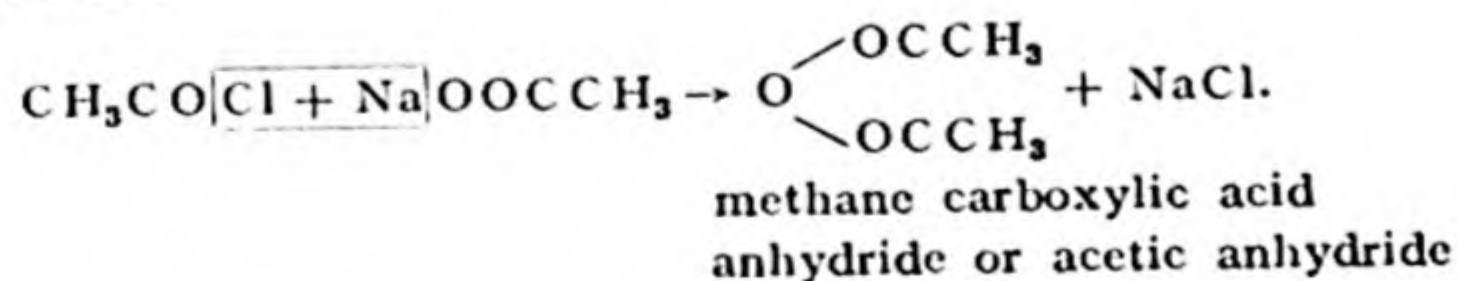
Acetyl derivatives are also produced by the action of acid chlorides on primary amines, the group $\text{R}-\text{C}=\text{O}$ being attached to nitrogen:



Acetyl chloride can therefore be used also for detecting the presence of an amino group.

(b) Acid anhydrides

76. These compounds are produced by treating alkali salts of fatty acids with acid chlorides:



This is the method of preparation for the lower acid anhydrides. The higher acid anhydrides are obtained in good yield by heating the sodium salts of the acids with *acetic anhydride*.

The acid chlorides may be considered as mixed anhydrides of hydrochloric acid and fatty acid, their formation from hydrogen chloride and fatty acid with P_2O_5 as dehydrating agent being in agreement with this opinion. Mixed anhydrides of fatty acids do actually exist but they split up into the anhydrides of the two acids on distillation.

TABLE 24
BOILING POINTS OF SOME ACID ANHYDRIDES

Name	Formula	B.p.
Acetic anhydride	$(CH_3C=O)_2O$	140.0°
Propionic anhydride	$(C_2H_5C=O)_2O$	167°
Butyric anhydride	$(C_3H_7C=O)_2O$	192°

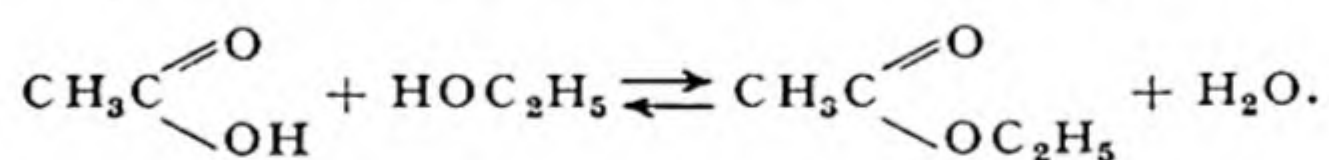
Acid anhydrides are unpleasant, pungent smelling liquids, which are miscible with water to a limited extent only.

The boiling points of the lower acid anhydrides are given in Table 24. The anhydride of formic acid is unknown.

Acetic anhydride is slowly converted into acetic acid by water at ordinary temperatures. This behaviour contrasts with that of acetyl chloride, which reacts very rapidly with water. Acetic anhydride can react with compounds containing hydroxyl or amino groups; with the former, esters are produced (77), whilst the latter give acetylamino-compounds.

(c) *Esters of organic acids*

77. We have mentioned already that esters are formed by the action of inorganic acids, (38) or acid chlorides or acid anhydrides on alcohols. Esters are also produced by the action of alcohols on organic acids:



This reaction is reversible as was first shown by BERTHELOT and PEAN DE ST. GILLES (1862). VAN 'T HOFF showed in 1877, that the experimental results obtained by BERTHELOT and ST. GILLES are in agreement with the law of mass action.

If the initial concentrations of alcohol and acid are represented by a and b , and the concentrations of ester (and water) present in the final state by x , all expressed in grammolecules per unit volume, then the following equation holds:

$$(a-x)(b-x) = Kx^2.$$

From observations it follows that the value of K is about 0.25 for the formation of ethyl acetate at 20°. Thus if one starts with a mixture of 1 mol of ethanol and 1 mol of acetic acid there is present in the reactions mixture

when equilibrium is reached, $\frac{2}{3}$ mol. of ester, $\frac{2}{3}$ mol. of water, $\frac{1}{3}$ mol. of acetic acid and $\frac{1}{3}$ mol. of alcohol. If 1 mol. of acetic acid and 0.05 mol. of alcohol are used, the equilibrium is reached at 0.049 mol. of ester; if 1 mol. of acetic acid to 8 mols. of alcohol are used, 0.945 mol. of ester is present at equilibrium.

The value of the equilibrium constant alters only very slightly with changes in temperature; in agreement herewith the calorific effect of ester formation is small.

At ordinary temperature the velocity of ester formation is very low, but it can be considerably increased by the catalytic action of anhydrous hydrochloric acid or of concentrated sulphuric acid. The preparation of an ester is usually carried out as follows.

A mixture of anhydrous acid and an excess of alcohol in which a few per cent. of hydrogen chloride or concentrated sulphuric acid have been dissolved, is warmed under a reflux condenser. The reaction mixture is then poured into water; the esters of the lower alkane carboxylic acids then separate as a liquid layer floating on the aqueous solution.

The velocity of esterification depends on the structure of the reacting substances. Under similar conditions primary alcohols are esterified more quickly than secondary. The velocity constant ($k \times 10^5$) for the esterification of various alcohols with trichloroacetic acid at 25° has the following values: 725 for propanol-1, 98 for propanol-2, 1200 for butanol-1, 90 for butanol-2 and 118 for trimethylmethanol or trimethylcarbinol $(\text{CH}_3)_3\text{COH}$. Therefore the velocities of esterification of secondary and tertiary alcohols do not differ markedly. $k \times 10^5 = 650$ was found for ethanol and $k \times 10^5 = 3690$ for methanol; the first alcohol of the series is esterified most rapidly therefore.

Esters can also be obtained by warming the silver salt of an acid with an alkyl iodide.

The esters of the lower alkane carboxylic acids are colourless liquids, which are only slightly soluble in water. Many have a pleasant odour reminiscent of fruits (use for the preparation of "fruit essences"). The boiling points of a few esters are given in Table 25.

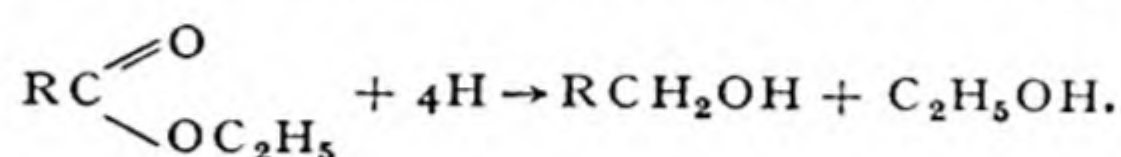
TABLE 25
BOILING POINTS OF SOME ESTERS

Name	Formula	B.p.
Ethyl formate	HCOOC_2H_5	54°
Ethyl acetate	$\text{CH}_3\text{COOC}_2\text{H}_5$	77°
<i>iso</i> Amyl acetate	$\text{CH}_3\text{COOC}_5\text{H}_{11}$	142°
Ethyl butyrate	$\text{C}_3\text{H}_7\text{COOC}_2\text{H}_5$	121.5°
Octyl acetate	$\text{CH}_3\text{COOC}_8\text{H}_{17}$	210°

The esters of the lower fatty acids and lower alcohols are good solvents for various organic substances; ethyl acetate and amyl acetate are used for technical purposes. Ethyl acetate is also used as the starting product for the synthesis of important substances like ethyl acetoacetate (see 148), antipyrine, (323), etc.

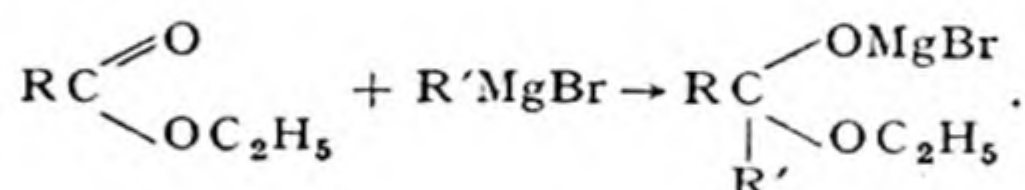
The various kinds of waxes consist chiefly of esters of higher fatty acids and higher alcohols. The chief constituent of bees' wax is myricyl palmitate, $C_{15}H_{31}COOC_{30}H_{61}$, spermaceti contains cetyl palmitate, $C_{15}H_{31}COOC_{16}H_{33}$. Carnauba wax, a vegetable wax, contains the myricyl ester of cerotic acid, $C_{25}H_{51}COOH$.

Esters can be converted into primary alcohols by reduction with sodium and absolute alcohol by the method of BOUVEAULT and BLANC:

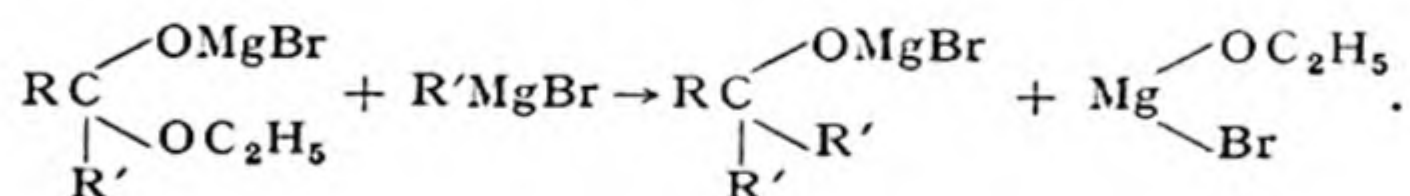


This reaction may also be carried out by catalytic reduction with the aid of copper chromite catalysts.

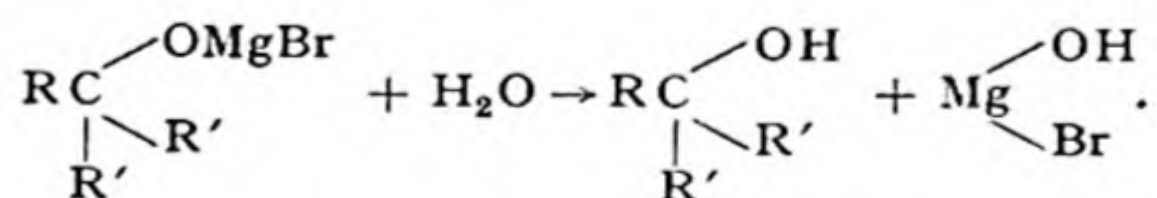
The interaction of alkylmagnesium compounds (54) on esters leads to tertiary alcohols:



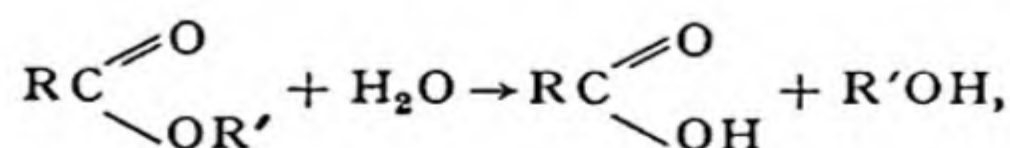
The addition product formed in this way then reacts with a second molecule of alkylmagnesium halide according to the equation:



and this second intermediate product is decomposed by water giving a tertiary alcohol:



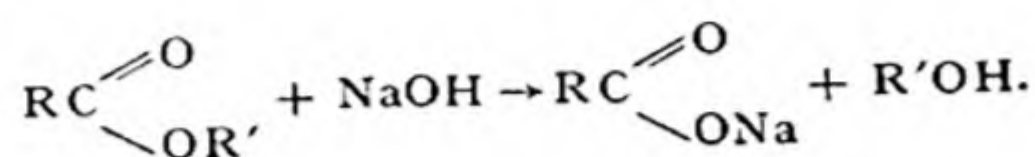
The *hydrolytic fission* of esters into alcohol and acid according to the equation



can be carried out by treating the ester with an excess of water and a small quantity of an acid, which acts as a catalyst. It has been found that the

velocity constant of the reaction is roughly proportional to the hydrogen-ion concentration to which the catalytic action can be attributed.

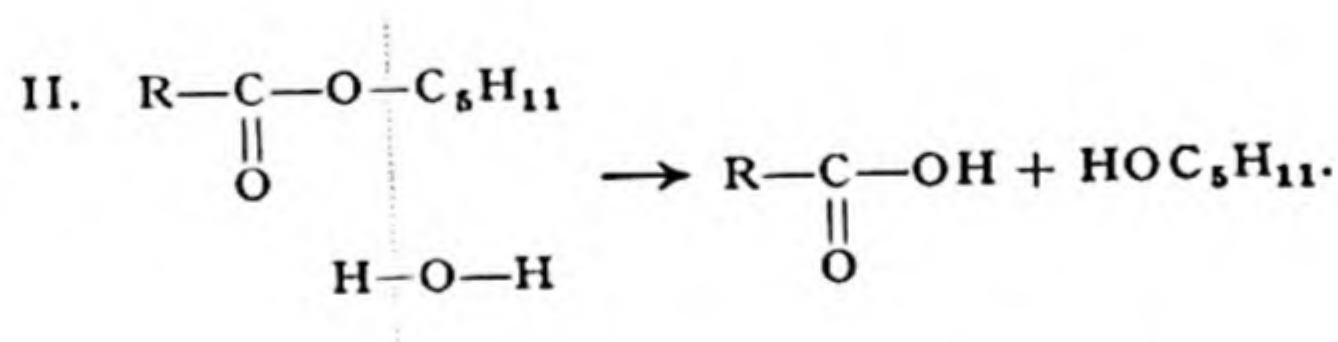
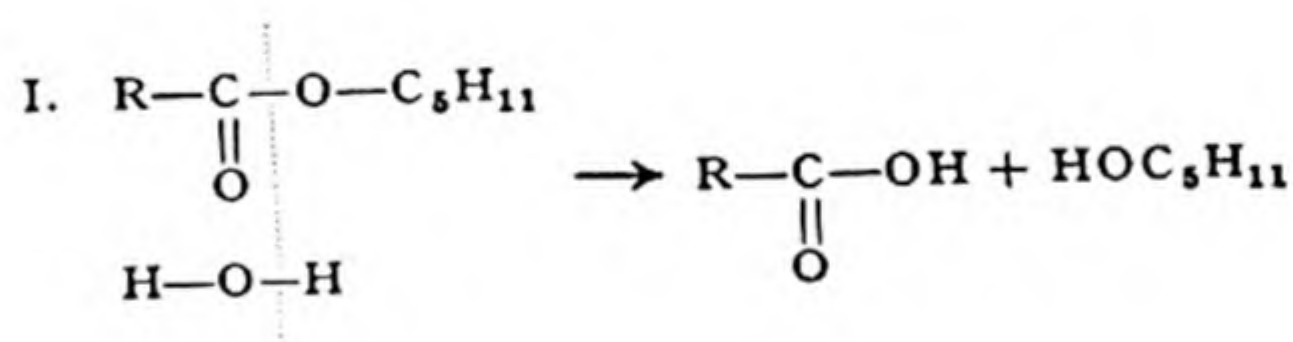
The fission of esters by alkalis, called "saponification", takes place according to the equation:



Decomposition of esters by dilute alkalis in general takes place much more rapidly than with dilute acids. The ratio of the velocity constants for the hydrolysis of methyl acetate in 0.1 *n*-solutions of KOH and HCl is found to be 1350.

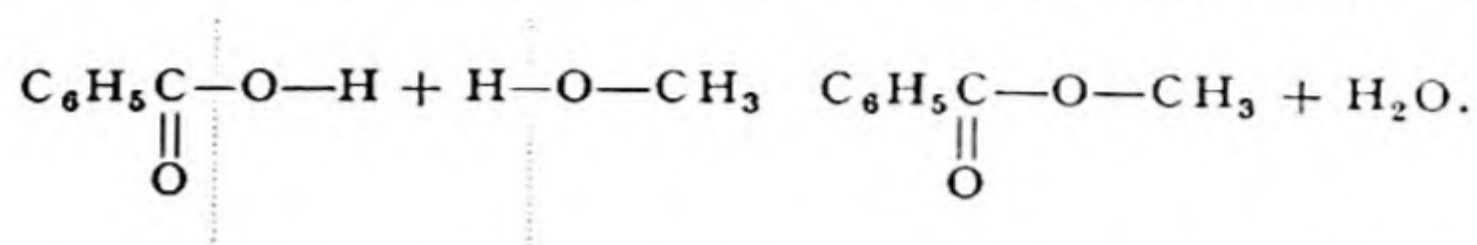
At the same concentration, strong bases decompose esters much more rapidly than weak bases; the velocity constant is roughly proportional to the concentration of hydroxyl-ions.

Two different mechanisms are conceivable for the hydrolysis of an ester; according to I (below) the bond between $\text{RC} \begin{array}{l} \text{O} \\ \parallel \\ \text{RCO} \end{array}$ and OC_5H_{11} is broken and in II the bond between $\text{RC} \begin{array}{l} \text{O} \\ \parallel \\ \text{RCO} \end{array}$ and C_5H_{11} .



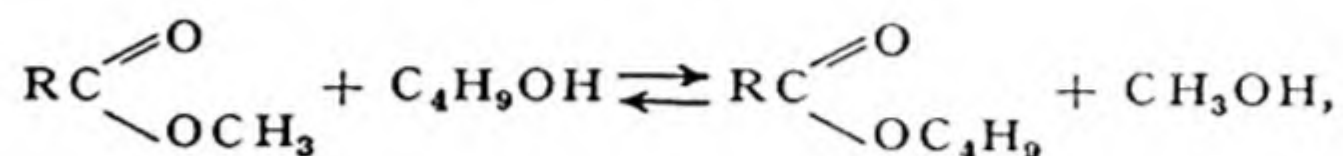
POLANYI and SZABO carried out the hydrolysis of amyl acetate with a dilute solution of sodium hydroxide in water containing a small quantity of H_2^{18}O (the content of ^{18}O isotope was 0.35 atom per cent. more than in ordinary water). The amyl alcohol obtained in this experiment was dehydrated by passing it over alumina at 400° ; a very accurate determination of the specific gravity of the water obtained, showed that it contained no ^{18}O . From this it follows that in the hydrolysis of the ester, the oxygen in the water does not appear in the alcohol. Hence hydrolysis takes place by mechanism I. In a similar way it has been shown that the acid hydrolysis of an ester by means of hydrochloric acid in water containing H_2^{18}O , takes place according to scheme I (INGOLD).

The esterification of benzoic acid takes place according to the equation:



In order to prove this, benzoic acid was esterified with methanol containing ^{18}O (0.37%); the water produced in this reaction contained no ^{18}O so that the oxygen of this water was derived from the benzoic acid and not from the methanol.

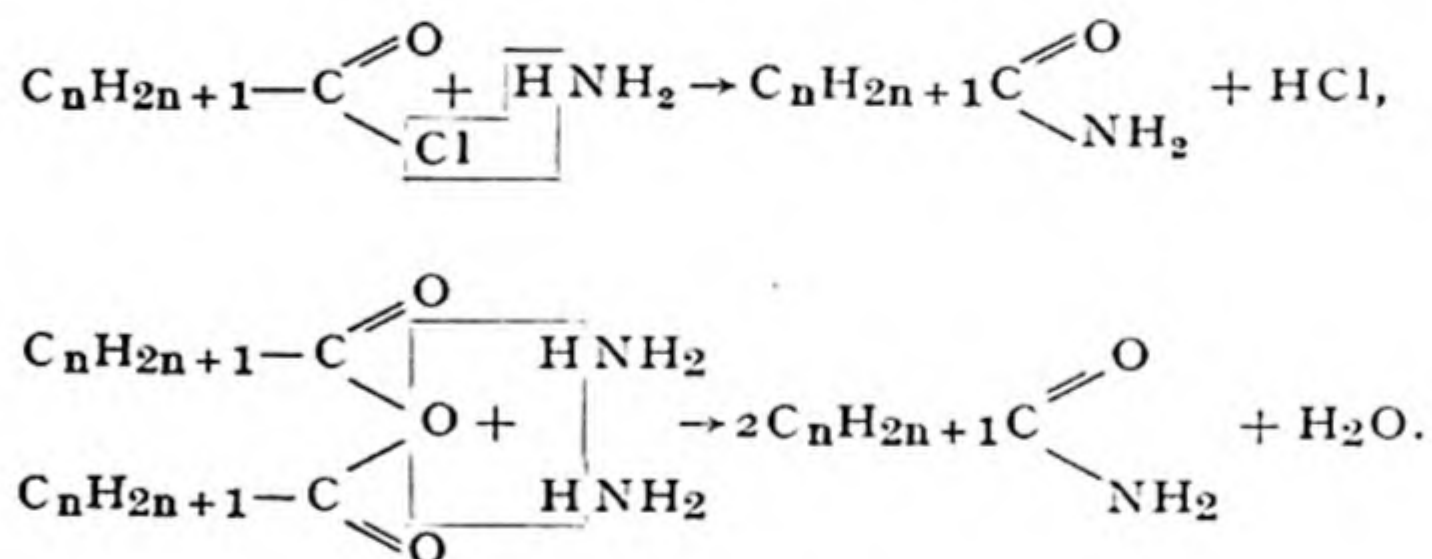
Not only can esters be decomposed by *hydrolysis*, *i.e.* by decomposition by the action of water, but they can be decomposed by *alcoholysis*, *i.e.* decomposition by the action of alcohol, *e.g.*:



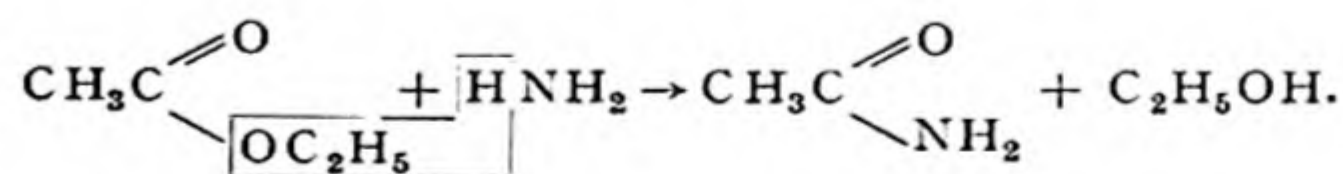
in which one alkoxy group displaces another. This reaction also is reversible and can take place at ordinary temperatures under the catalytic influence of a small amount of sodium alcoholate or acid.

(d) *Carbonamides or acid amides* $\text{C}_n\text{H}_{2n+1}\text{C}(=\text{O})\text{NH}_2$

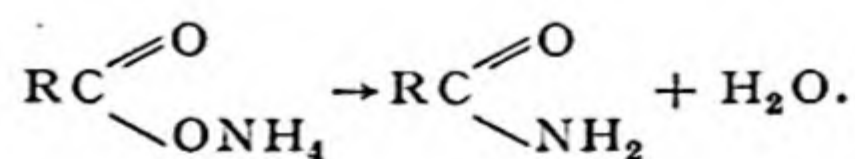
78. These compounds may be formed by the action of ammonia on acid chlorides or acid anhydrides, from which reactions the structure is apparent:



Carbonamides are also obtained when anhydrous ammonia is allowed to react on esters:



Amides are also produced by heating ammonium salts of carboxylic acids, a molecule of water being split off in the process:



It has already been mentioned in 66 that the carbonamides can be considered as intermediate products in the conversion of carbonitriles into acids. When carbonitriles are dissolved in concentrated sulphuric acid or in concentrated hydrochloric acid at ordinary temperatures, acid amides are produced. Also the action of an alkaline solution of hydrogen peroxide on carbonitriles leads to the formation of amides. Conversely, carbonamides can be converted into carbonitriles by the action of dehydrating agents such as phosphorus pentoxide.

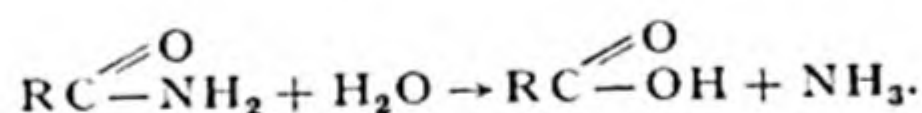
The melting points and boiling points of a few acid amides are given in Table 26.

TABLE 26
MELTING AND BOILING POINTS OF SOME ACID AMIDES

Name		Formula	M.p.	B.p.
	Formamide	HCONH ₂	2.55°	105° at 11 mms
Methane carbonamide	Acetamide	CH ₃ CONH ₂	82°	221°
Ethane carbonamide	Propionamide	C ₂ H ₅ CONH ₂	79°	222°
Propane carbonamide	Butyramide	C ₃ H ₇ CONH ₂	116°	216°
Heptadecane carbonamide	Stearamide	C ₁₇ H ₃₅ CONH ₂	109°	—

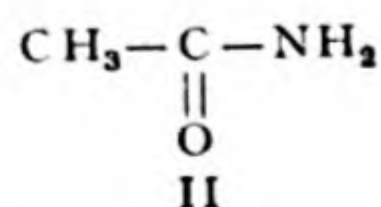
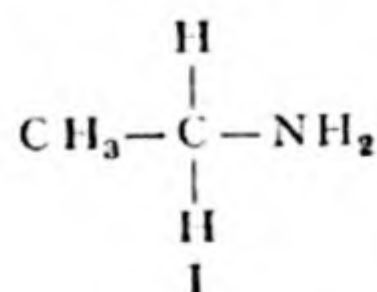
Formamide is miscible in all proportions with water and ethyl alcohol; *acetamide* is very readily soluble in these solvents.

Acid amides can be decomposed into the carboxylic acid and ammonia by water:



The hydrolytic fission of acid amides occurs on warming these substances with dilute acids or with dilute alkalis; the hydrolysis is slower in the latter case.

Thus in acid amides the bond between the carbon atom and the nitrogen atom can be easily broken, but not in the primary amines. When the structure of the acid amides is compared with that of the primary amines with the same number of carbon atoms,



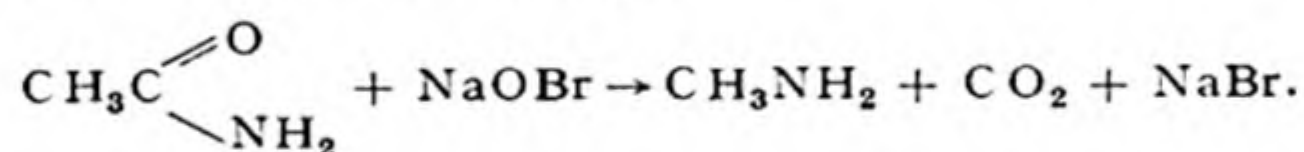
it is apparent that the bond between the carbon atom and the nitrogen atom is far less firm, since this carbon atom is attached at the same time to an oxygen atom by a double bond. A similar state of affairs has already been noted with the acid chlorides, which are much more easily decomposed by

water than the alkyl chlorides. Acid amides may also be considered as ammonia in which a hydrogen atom is replaced by an acid, or *acyl* residue $R-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$. As a result of this substitution the basic properties of ammonia disappear to a great extent. Acid amides can still form salts but these salts are already decomposed by water at ordinary temperatures. The hydrochloride of acetamide, $\text{CH}_3\text{CONH}_2\cdot\text{HCl}$, is produced by passing gaseous hydrogen chloride into an ethereal solution of the amide.

The hydrogen atoms in the amido group in acid amides can be substituted by metals; by the action of sodamide on an ethereal solution of an acid amide, a compound $R-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{NHNa}$ is produced, but it is decomposed immediately by water. The mercury compounds, such as $(\text{CH}_3\text{CONH})_2\text{Hg}$, produced by the action of mercuric oxide on acetamide, for example, are more stable.

Amides are converted into the corresponding carboxylic acids by the action of nitrous acid; the NH_2 -group is replaced by $-\text{OH}$ and nitrogen and water are produced. Thus this reaction takes a similar course to the action of nitrous acid on primary amines.

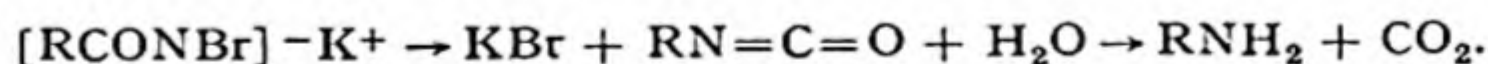
The change which amides of alkane carboxylic acids and of aromatic acids undergo by the action of bromine and alkali, is important; primary amines (46) are produced containing *one carbon atom less* than the acid amide from which they are derived. (HOFMANN):



HOOGEWERFF and VAN DORP have improved the method of carrying out the HOFMANN reaction by using a solution of NaOCl (NaOBr or bleaching powder).

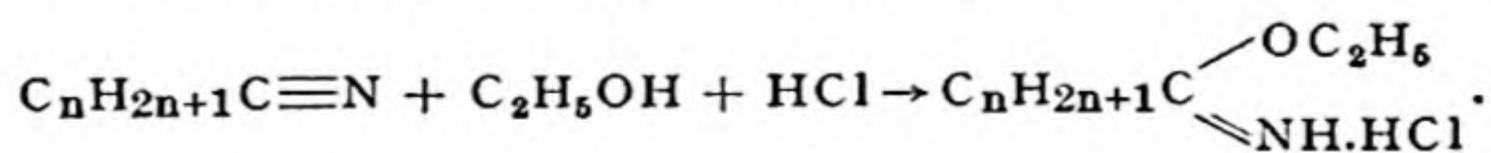
The initial product to be produced and isolated is an amide brominated on the nitrogen atom: $\text{RCONH}_2 \rightarrow \text{RCONHBr}$ or RC(OH)=NBr .

The hydrogen atom in acid amides, which is easily replacable by metals under the influence of the acyl residue, is replaced even more readily under the added influence of the bromine atom. In the presence of potash a *potassium bromoamide* is produced, a substance which is unstable, but which HOOGEWERFF and VAN DORP were able to isolate. Potassium bromide is split off from this compound, an intramolecular rearrangement takes place simultaneously to produce an ester of isocyanic acid (56, 156), which is eventually split up in the alkaline medium into a primary amine and carbon dioxide:

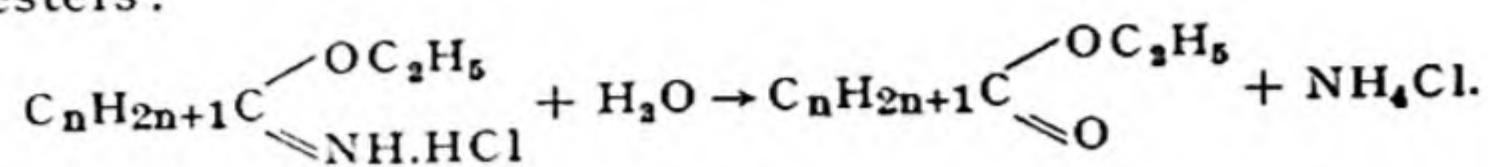


It is not known how the intramolecular transformation occurs. An optically active amine RNH_2 is obtained from an optically active amide containing an asymmetric group R and racemisation does not occur.

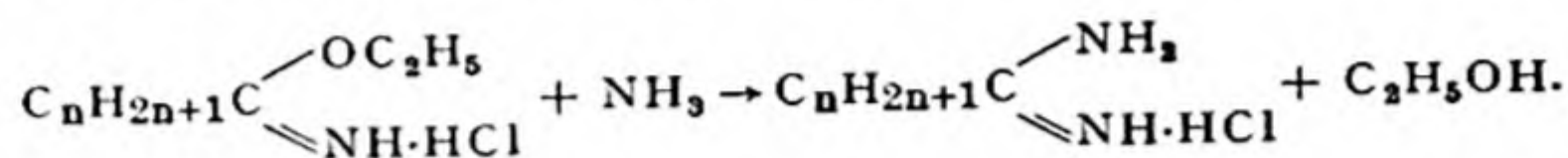
Iminoethers. When a mixture of a carbonitrile and alcohol is treated with a hydrogen halide in the absence of water, the hydro-halide of an iminoether is produced, *e.g.*:



These salts, which are usually well crystallised, are decomposed by water with the formation of esters:

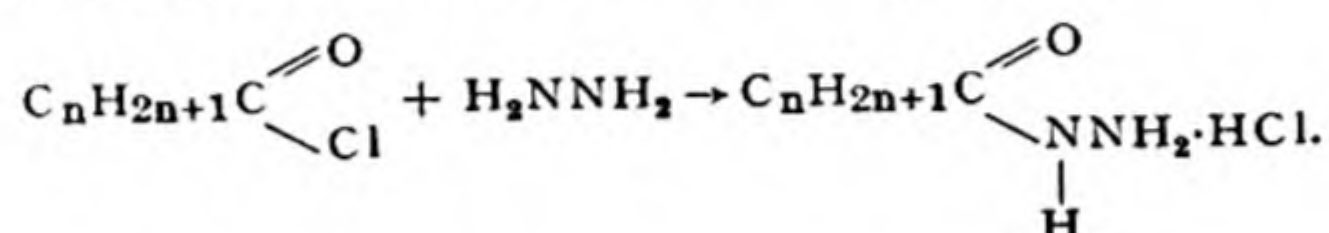


By the action of alcoholic ammonia, the group OC_2H_5 is replaced by NH_2 and the hydrochloride of an *amidine* (carbonamidine) is produced:



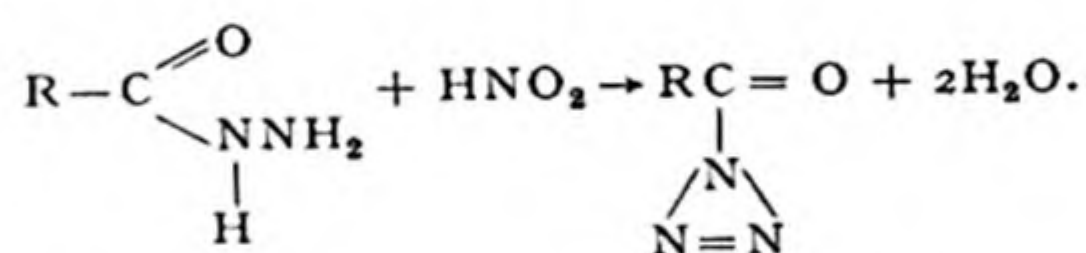
The amidines are basic substances, which form well crystallised salts with one equivalent of acid.

Acid hydrazides (*carbonhydrazides*) are substances, which are produced by the action of hydrazine on acid chlorides or esters (CURTIUS):



The hydrazides are basic substances which have reducing properties like most derivatives of hydrazine and are soluble in water.

Acid azides (*carbonazides*) are produced by the action of nitrous acid on acid hydrazides (CURTIUS):

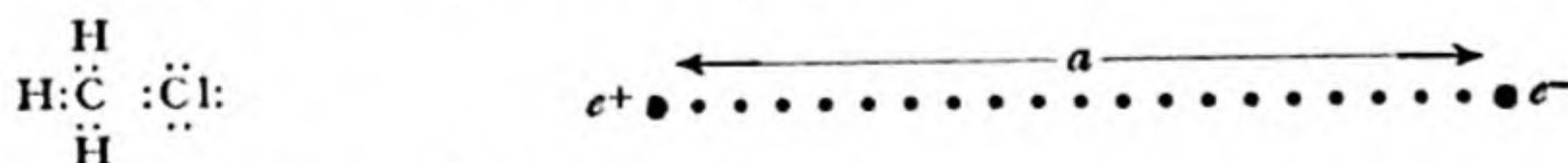


These acid azides, which frequently crystallise well, are in most cases rather unstable. On the formation of primary amines from acid azides see 152.

79. Dipole moments and polar molecules.

It may be deduced from the tetrahedral structure of methane that the mean position of the positive charges in the molecule must coincide with the mean position of the negative charges, so that methane would be expected to possess no dipole moment.

When a hydrogen atom in methane is replaced by a chlorine atom, however, the pair of electrons in chloromethane responsible for the bond between the chlorine atom and the carbon atom, will lie closer to the nucleus of the chlorine atom than to that of the carbon atom, because the chlorine atom exerts a greater attraction for electrons than the carbon atom. Therefore, in the molecule of chloromethane, the electron density is greatest in the neighbourhood of the chlorine atom; the mean position of the positive and negative charges no longer coincide but are separated by a distance a .



Electronic formula for chloromethane

The bond between carbon and chlorine is no longer a purely homopolar bond but an intermediate form between a homopolar and a heteropolar bond. If e represents

the numerical value of the total positive or negative charge, the molecule then possesses an electric moment called a *dipole moment* and the magnitude of the dipole moment is given by the product of the charge \times the distance, $\mu = a \times e$.

The size of an elementary electric charge is 4.77×10^{-10} electrostatic units. The distance a is of the order of magnitude of an Ångström unit. From this it follows that dipole moments are of the order of magnitude of 10^{-18} electrostatic-cm.-units (Debye units). Molecules possessing an electric moment are called *polar molecules*.

From the theory of polar molecules developed by DEBIJE it follows that the value of the dipole moment of a molecule can be calculated from the change of the dielectric constant with the temperature.

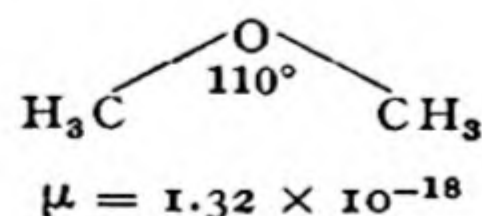
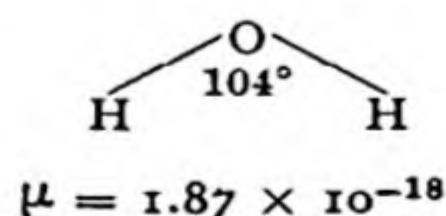
TABLE 27
VALUES OF THE DIPOLE MOMENTS OF VARIOUS ALIPHATIC COMPOUNDS
The numerical values are multiplied by 10^{18}

CH ₃ Cl	1.97	CH ₃ NH ₂	1.31
CH ₃ CH ₂ Cl	1.98	CH ₃ CH ₂ NH ₂	1.31
CH ₃ Br	1.82	CH ₃ COCH ₃	2.71
CH ₃ CH ₂ Br	1.86	CH ₃ CH ₂ COCH ₃	2.79
CH ₃ OH	1.73	(CH ₃) ₃ CCOCH ₃	2.79
CH ₃ CH ₂ OH	1.68	HCOOH	1.20
CH ₃ CH ₂ CH ₂ OH	1.69	CH ₃ COOH	0.8
		CH ₃ CH ₂ COOH	0.8

All the alkyl chlorides have practically the same value for their dipole moments and so have the alkyl bromides; this is also the case for primary alcohols, ketones and amines. Apparently the value of the dipole moment is independent of the size of the alkyl residue and is determined chiefly by the nature of the polar groups or atoms, Cl, Br, OH, NH₂, CO, etc. If formic acid is excepted, the same holds for the alkane carboxylic acids (see Table 27).

Hence the dipole moment of the above mentioned molecules may be considered as being localised between the polar group and the rest of the molecule; by the dipole moment of an atom or group of atoms, *e.g.* halogen, OH, NH₂, CO, COOH, in aliphatic compounds is meant the moment of the dipole between one of these groups and the group C_nH_{2n+1}.

Because both water and the ethers possess a dipole moment, their structures cannot be linear but the angle between the oxygen bonds must be smaller than 180°. The size of the angle may be calculated as about 104° for water and about 110° for dimethyl ether,



Non-polar character of the alkanes. From a comparison of the dipole moments of benzene and toluene it may be deduced in the following way that a small dipole moment is to be ascribed to the C-H bond. The dipole moment of benzene is zero; this is to be expected since the electrical charges are symmetrically situated in the structure model (regular flat hexagon 214). The dipole moment of toluene, C₆H₅CH₃,

is 0.4×10^{-18} ; this is the moment of the CH_3 -group with regard to the phenyl-group. It is easily deduced from the tetrahedral model for methane, that the vectorial sum of the moments of the C-H bonds in CH_3 is equivalent to the moment of the C-H bond. If one imagines that a hydrogen atom in methane is replaced by a methyl group, then the dipole moment remains unaltered, so that all homologues of methane must possess a dipole moment of zero. This has been confirmed experimentally by accurate measurements on a number of normal and branched chain alkanes.

It is clear that when all the hydrogen atoms in methane are replaced by chlorine, the dipole moment remains zero, while the compounds produced by replacing 1, 2 or 3 hydrogen atoms by chlorine must possess dipole moments. It is found that $\mu = 1.97 \times 10^{-18}$ for CH_3Cl , $\mu = 1.57 \times 10^{-18}$ for CH_2Cl_2 and $\mu = 0.95 \times 10^{-18}$ for CHCl_3 .

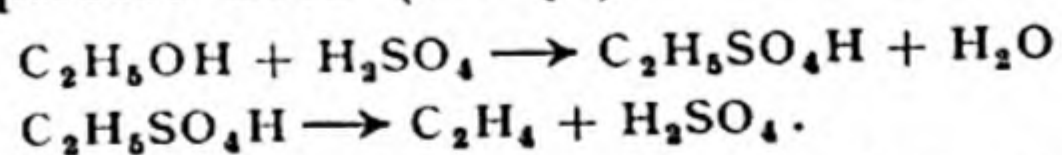
(x) UNSATURATED HYDROCARBONS

80. Two series of hydrocarbons are known in which the composition agrees with the general formula C_nH_{2n} . Thus these substances contain two atoms of hydrogen less than the saturated hydrocarbons with the same number of carbon atoms. Also, hydrocarbons are known which contain still fewer atoms of hydrogen compared with the number of atoms of carbon, *e.g.* a series with the general formula $\text{C}_n\text{H}_{2n-2}$, and also a series represented by $\text{C}_n\text{H}_{2n-4}$. The hydrocarbons in these various groups contain an *even* number of atoms of hydrogen less than the saturated hydrocarbons with the same number of carbon atoms. This is in agreement with the even number of atoms rule (25). Two groups of hydrocarbons C_nH_{2n} are to be distinguished: the *alkenes* and the *cyclanes* (286).

(a) Alkenes

Methods of forming alkenes (C_nH_{2n}).

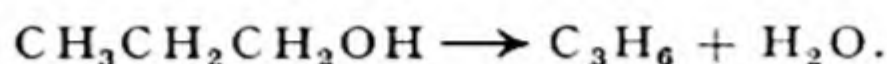
1. The alkenes are produced by the splitting off of water from alcohols, *e.g.* by heating the alcohol with dehydrating agents such as strong sulphuric acid, anhydrous oxalic acid or zinc chloride. In the formation of ethene (ethylene) by heating a mixture of ethanol and an excess of sulphuric acid, ethylsulphuric acid is first produced, which breaks down on further heating into ethene and sulphuric acid (cf. 41).



At the temperature necessary for the formation of ethene, carbonisation also occurs, with the consequent production of sulphur dioxide and carbon dioxide, which are removed by washing with dilute alkali.

With alcohols with 7-12 carbon atoms the fission takes place easily when a mixture of the alcohol with 5-10 % of strong sulphuric acid or with 1 % of naphthalene sulphonic acid (281) is heated, the resultant alkene and water being removed by distillation (SENDERENS). Secondary and tertiary alcohols lose water more easily than primary alcohols.

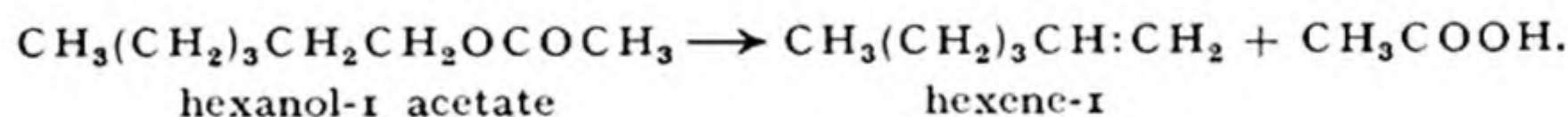
Ethene and propene are best prepared by a catalytic method in which ethanol or propanol vapour is led over aluminium oxide or anhydrous aluminium sulphate at 350–400°. The alcohol is decomposed quantitatively into alkene and water:



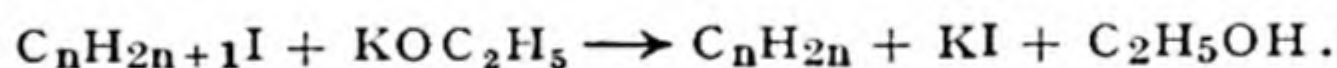
This catalytic decomposition of alcohols was discovered in 1795 by the "Dutch Chemists" (DEIMAN, PAETS VAN TROOSTWIJK, LAUWERENBURGH and VROLIK), who obtained "oliphant gas" (ethene), for example, by passing alcohol vapour through a hot tube filled with alumina; they noticed that if an empty glass tube were used for the experiment, it was necessary to heat to a higher temperature to decompose the alcohol and very little oliphant gas was produced. This catalytic reaction was investigated more closely by various investigators (IPATIEW, SENDERENS, SABATIER) about a century later. When it is remembered, that in the presence of finely divided copper, alcohol is dehydrogenated—within approximately the same range of reaction temperatures—it is again apparent how the nature of the catalyst can influence the course of the reaction.

A mixture of alkenes is produced by the catalytic decomposition of the higher alcohols because the double bond wanders under the influence of the catalyst; a mixture of butene-1 and butene-2 is produced from butanol-1.

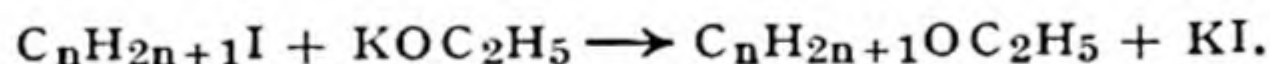
A good method of preparation for the higher alkenes exists in the thermal decomposition of the acetates or the stearates of the corresponding alcohols; no displacement of the double bond takes place in this reaction:



2. Splitting off of hydrogen halide from alkyl halides. This takes place by warming with alcoholic potash (a solution of potash in alcohol):



With primary alkyl halides ether is also formed under these conditions according to the equation:



With secondary and tertiary alkyl halides only alkene formation occurs.

Another method of preparing pure ethene is by treating 1,2-dibromoethane ($\text{C}_2\text{H}_4\text{Br}_2$), dissolved in aqueous alcohol, with a zinc-copper couple; two bromine atoms are taken out of the dibromoethane (GLADSTONE and TRIBE).

3. Alkenes are produced by thermal decomposition of alkanes (see 26); ethene and some of its homologues are formed in the dry distillation of coal, hence coal gas contains about 2 % of ethene.

81. Nomenclature of the alkenes. The names of these hydrocarbons are formed by replacing the suffix "ane" in the saturated hydrocarbons by "ene": *ethene*, *propene*, *hexene*, etc. The general name therefore is *alkenes*.

The name *olefine*, used earlier for this group of compounds, is connected with the name "oliphant gas", which was given by the discoverers of ethene to this substance, because they observed that a liquid ($C_2H_4Cl_2$) having the appearance of oil was produced by the action of chlorine on ethene.

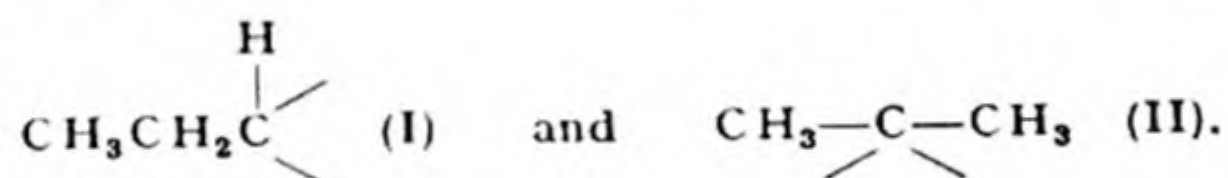
The names ethylene, propylene, etc. are still used.

Structure. Various assumptions can be made as to the distribution of the bonding forces in an alkene C_nH_{2n} .

1. The molecule contains a carbon atom with two free valency bonds (or a bivalent carbon atom). The structure of ethene would then be represented by $H_3C.CH<$.

The dichloroethane $C_2H_4Cl_2$ which is readily produced by the combination of 1 molecule of ethene with 1 molecule of chlorine, must then be 1,1-dichloroethane, CH_3CHCl_2 . 1,1-Dichloroethane, which can be prepared by

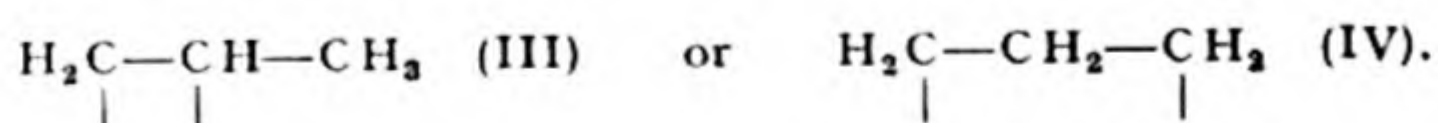
the action of phosphorus pentachloride on ethanal (63), $CH_3\overset{H}{\underset{|}{C}}=O$, however, is different from the dichloroethane produced by addition of chlorine to ethene. On the assumption of two free valency bonds, two structures can be written for propene:



1,1-Dichloropropane, $CH_3CH_2CHCl_2$, should be produced from propene and chlorine if structure I is to be attributed to propene and 2,2-dichloropropane, $CH_3CCl_2CH_3$, if propene is represented by II. 1,1-Dichloropropane and

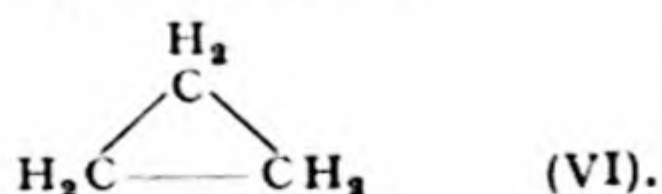
2,2-dichloropropane, which can be prepared from propanal, $CH_3CH_2\overset{H}{\underset{|}{C}}=O$, and acetone, $(CH_3)_2C=O$, respectively, are different however from the dichloropropane produced from propene and chlorine. Hence the assumption made under 1 must be rejected.

2. The molecule of an alkene contains two carbon atoms each with a free valency bond (or two trivalent carbon atoms), which would lead to two structural formulae for propene:



3. The molecule contains a carbon double bond, $H_3C-\overset{H}{\underset{|}{C}}=CH_2$ (V).

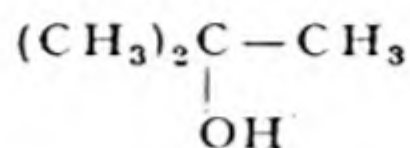
4. The molecule has a ring structure:



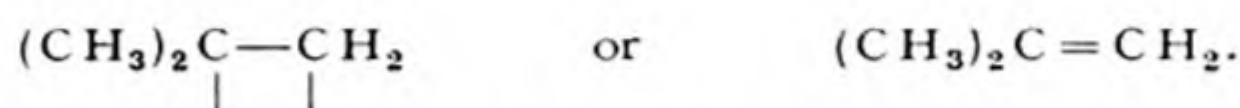
Propene is produced by splitting off hydrogen iodide both from 1-iodo-

propane, $\text{CH}_3\text{CH}_2\text{CH}_2\text{I}$ and from 2-iodopropane, $\text{CH}_3\text{CHICH}_3$. Structures IV and VI are excluded by this latter method of formation. The fact that propene can be formed by splitting off water from either propanol-1 or propanol-2 also leads to the rejection of structural formulae IV and VI.

Isobutene, C_4H_8 , is produced from both $(\text{CH}_3)_2\text{CHCH}_2\text{OH}$ and

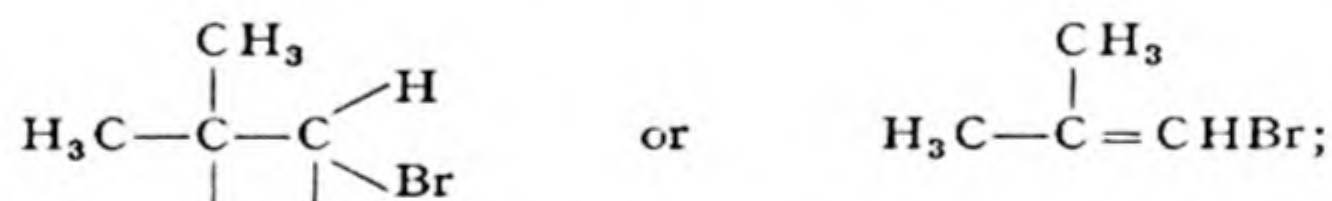


by removal of water, as well as from the butyl iodides, $(\text{CH}_3)_2\text{CHCH}_2\text{I}$ and $(\text{CH}_3)_3\text{CI}$, corresponding with these butanols, by elimination of a molecule of hydrogen iodide. Hence two structural formulae come into consideration for isobutene:



In general, the following empirical rule is valid: *when hydrogen halide is removed from an alkyl halide, or water from an alcohol, the hydrogen atom and the halogen atom or the hydroxyl group, respectively, are removed from two adjacent carbon atoms.* The correctness of this rule is apparent from the following example.

A dibromobutane having the structure $\text{CH}_3-\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}-\text{CH}_2\text{Br} \\ | \\ \text{Br} \end{array}$, is produced by the addition of bromine to isobutene. A molecule of hydrogen bromide can be split off from this compound with the production of 2-methyl-1-bromopropene-1:



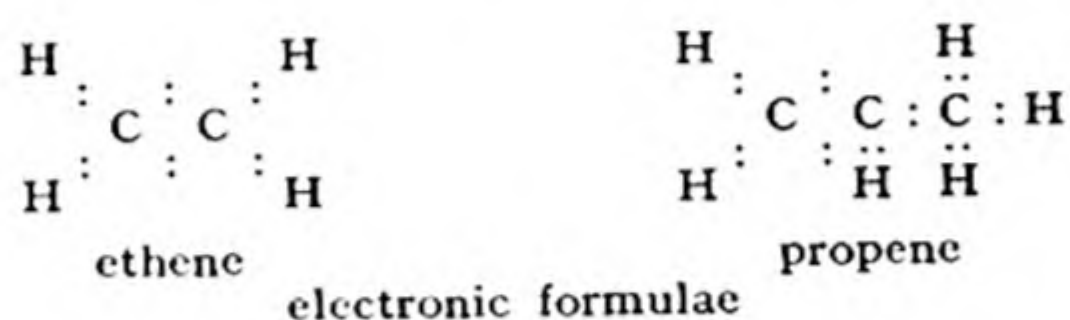
the formation of acetone on oxidation is in agreement with both these structures. It is not possible, however, to remove hydrogen bromide from the 2-methyl-1-bromopropene-1 since it cannot occur from two adjacent carbon atoms.

Thus the structure of the alkenes can be represented by the formula $\begin{array}{c} \text{H} \quad \text{H} \\ | \quad | \\ \text{R}-\text{C}-\text{C}-\text{R}' \\ | \quad | \end{array}$, in which two free bonding forces occur on adjacent carbon atoms or by the formula $\begin{array}{c} \text{H} \quad \text{H} \\ | \quad | \\ \text{R}-\text{C}=\text{C}-\text{R}' \end{array}$, in which a double bond is present between two carbon atoms.

If the presence of two free bonding forces is assumed, then a second assumption must be made, that these free bonding forces must occur on adjacent carbon atoms in the molecule of an alkene; the assumption of a carbon double bond is therefore simpler.

In the electronic formula a free bonding force would correspond with an unshared electron. Indeed compounds in which an unshared electron occurs, are known. These are the free radicals like CH_3 , C_2H_5 , (see 89). The properties of these substances are totally different from those of the alkenes.

For these reasons it is assumed that there is a double bond between two adjacent carbon atoms in the molecule of an alkene, which is brought about by two pairs of electrons; the electrons in each pair have opposite spins.



Ethene shows a dipole moment of zero; this is in agreement with the accepted structure in which the electric charges are distributed symmetrically.

Stereochemistry of the carbon double bond

82. In VAN 'T HOFF's stereochemical theory two doubly bound carbon atoms were represented by two tetrahedra having one side in common, Fig. 23 or Fig. 22, in which the bonding forces of the carbon atoms are drawn.

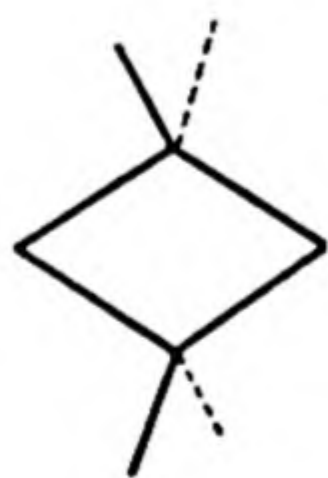


Fig. 22.
Stereoformula for ethene

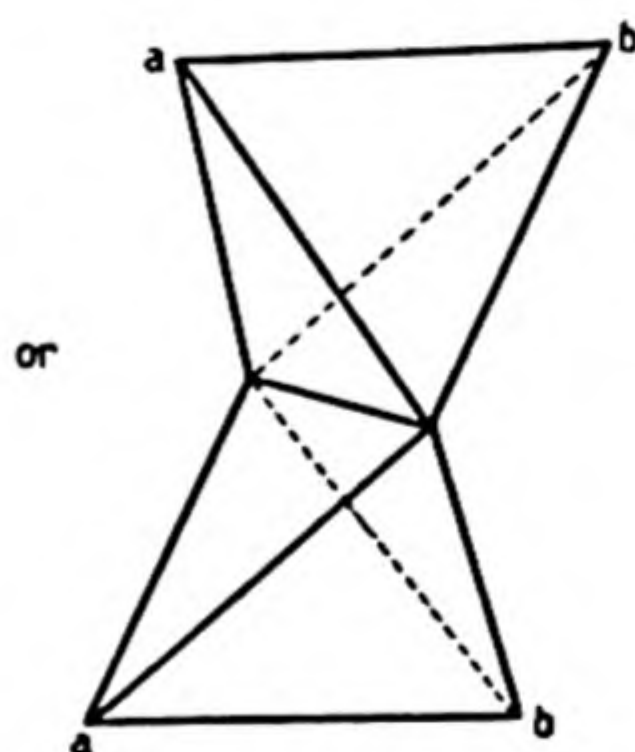


Fig. 23.

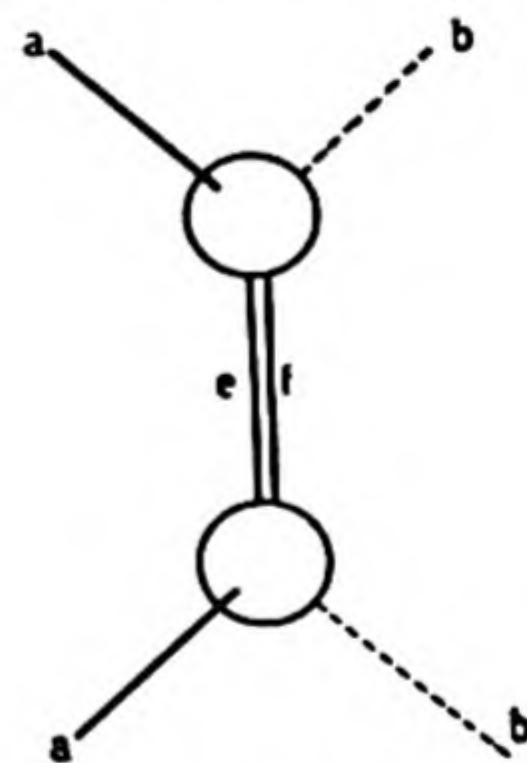


Fig. 24. A. VON BAEYER'S
representation of ethene

The stereoformula for ethene is given in Fig. 22. The bonding forces of the double bond lie in the plane of the drawing, the C—H bonds lie in pairs in front of and behind this plane. A. VON BAEYER modified this method of representation by supposing that the bonding forces in the double bond were distributed parallel with the line joining the centres of mass of the carbon atoms (Fig. 24). In the molecule of a saturated hydrocarbon, the

angle between the bonding forces is $109^{\circ}28'$. The bonding forces in the double bond are deflected from the original direction by an amount equal to $54^{\circ}44'$. VON BAEYER assumes that this produces a "strain" in the molecule, which tends to bring the bonding forces back to their original position. This strain should be the origin of the additive power of the double bond. According to this hypothesis, the so called *strain theory* of VON BAEYER (1885), molecules in which the directions of the C—C bonds deviate to a marked extent from the tetrahedral configuration, easily undergo reactions by which the tetrahedral arrangement is restored. In BAEYER's hypothesis the idea of strain was not associated with any particular physical significance. Notwithstanding this formal character, the strain theory of BAEYER is able to provide a qualitative explanation of the chemical behaviour of many cyclic compounds (see, for example, 288).

It is assumed that two singly bound carbon atoms (Fig. 25) are free to rotate around the common bond, because compounds of the type XCH_2CH_2X or XCH_2CH_2Y do not occur in isomeric forms. Since doubly bound carbon atoms are bound by two bonding forces, these atoms will not be freely rotatable about the common bond; for this to happen it will be necessary to break one of the bonds. Therefore, one would expect compounds of the type $aHC=CHa$ or $bHC=CHa$ to exist in two isomeric forms, in which the similar groups lie on the same side of the plane *ef* of the double bond, *cis-configuration* (Fig. 26), or in which these groups lie on opposite sides, *trans-configuration* (Fig. 27) (VAN 'T HOFF, 1874; WISLICENUS).

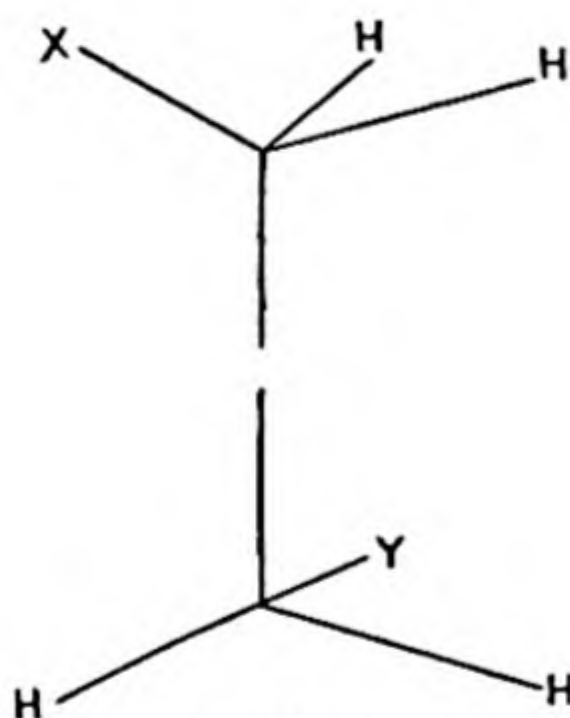


Fig. 25. Single bond;
free rotation possible

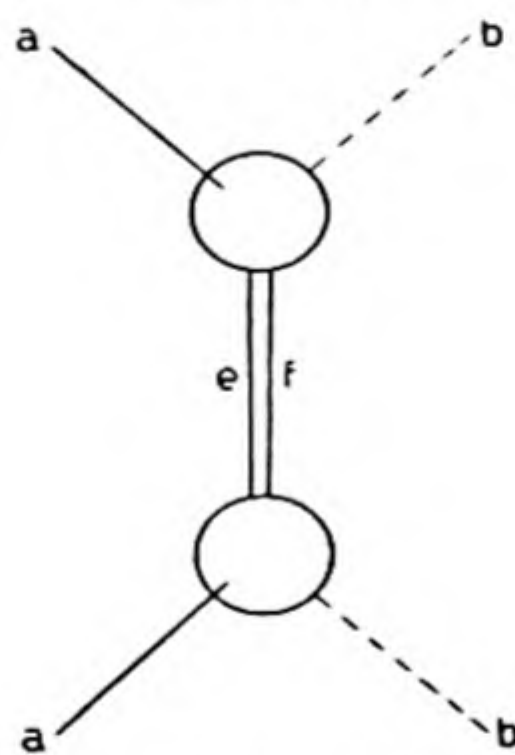


Fig. 26.
Double bond; *cis* and *trans* configuration.
No free rotation possible

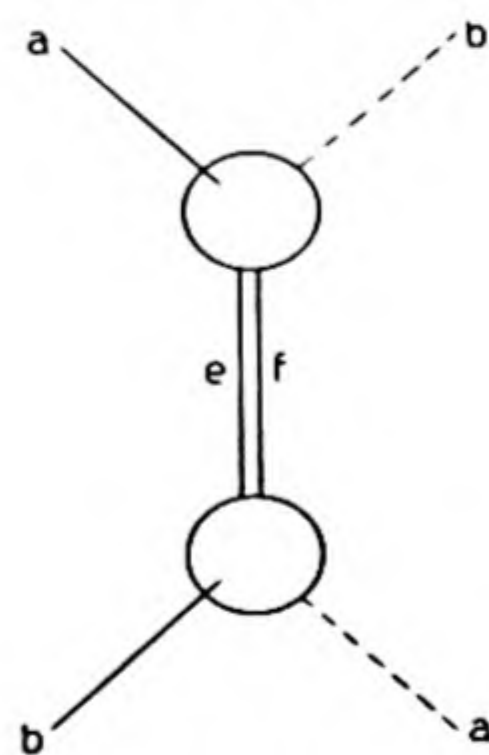
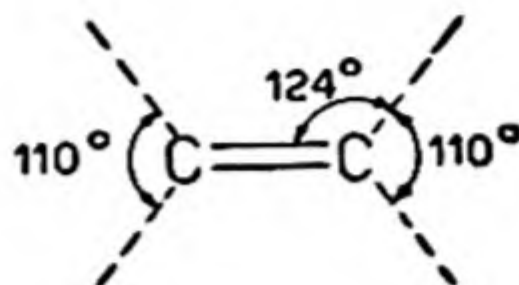


Fig. 27.

A large number of stereoisomers of this type are known (see 126).

According to the wave-mechanical theory of the chemical bond the two pairs of electrons in the carbon double bond are associated in different states. One pair, called σ -electrons, form the C—C bond corresponding with the C—C bond in the alkane. The orbitals of these σ -electrons lie in the plane in which,—for example, in ethene—the hydrogen atoms and the carbon atoms are situated. From electron diffraction

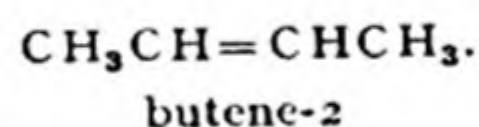
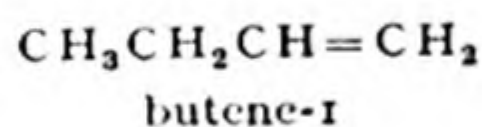
measurements in *isobutene*, the value $124^\circ (\pm 1^\circ)$ is derived for the angle between the double bond and the single bond.



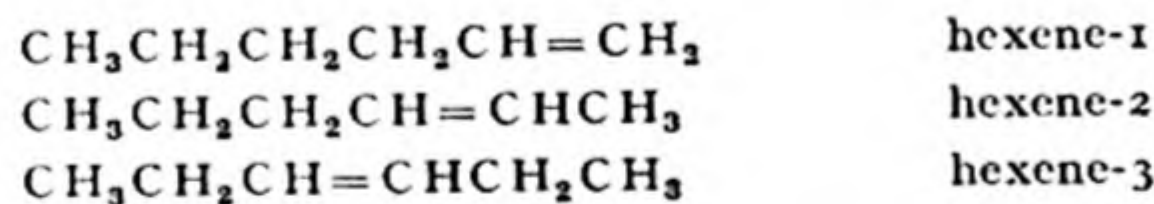
Each of the electrons of the other pair, called π -electrons, have orbitals which project above and below the plane of the molecule. These π -electrons form the second or π - π bond between the carbon atoms; according to the theory this second bond is not as strong as the first. Thus a difference is postulated between the two bonding forces of the double bond, contrary to the classical structure theory in which both bonding forces were considered equal. Since the π - π bond is weaker than the σ - σ bond, the former will be easily broken, which is the cause therefore of the additive power of the unsaturated hydrocarbons.

From the wave-mechanical theory it follows that rotation of halves of the molecule around the $C=C$ bond is considerably hindered, that is to say, that this rotation will require a high activation energy.

83. Isomerism. Butene is the first member of the series of alkenes in which isomerism can occur by virtue of the position of the double bond in the carbon chain. Two isomers are possible for a butene with a normal carbon chain; both are known and are differentiated as butene-1 and butene-2.



Thus the position of the double bond is indicated by the number of the first carbon atom attached to the double bond. All three possible structural isomers for unbranched hexenes are known.



A second cause of isomerism is to be found in the branching of the carbon chain. Besides the above mentioned butenes, a third isomer also is known, namely, *isobutene*, $(\text{CH}_3)_2\text{C}=\text{CH}_2$.

On account of these various causes a large number of isomers is possible in the higher alkenes; in many cases only a few of these isomers have been obtained in a state of purity.

84. Physical properties of the alkenes. Some of the more important physical constants of a number of alkenes are given in Table 28.

TABLE 28
SOME PHYSICAL CONSTANTS OF ALKENES

Name	Formula	B.p. (760 mm) °C	M.p. °C	Density d_4^{20}	Heat of combustion, kcal/mol. at 25°C. under const. pressure related to liquid H ₂ O and gaseous CO ₂ (ROSSINI)
Ethene	C ₂ H ₄	—103.7	—169.5	$d_4^{102.4} = 0.6104$	337.2
Propene	C ₃ H ₆	— 47.6	—185.25	$d_4^{47.7} = 0.6104$	492.0
Butene-1	C ₄ H ₈	— 6.4	—185.35	$d_4^{6.47} = 0.6255$	649.8
Pentene-1	C ₅ H ₁₀	30.1	—166.1	0.6406	806.9
Hexene-1	C ₆ H ₁₂	63.5	—138	0.6736	964.3
Heptene-1	C ₇ H ₁₄	93.6	—119.1	0.6972	1121.7
Octene-1	C ₈ H ₁₆	121.5	—104	0.7151	1279.1
Nonene-1	C ₉ H ₁₈	147	—	0.7293	1436.6
Decene-1	C ₁₀ H ₂₀	171	—	0.7408	1594.0
Undecene-1	C ₁₁ H ₂₂	188–190	—	0.763	1751.5
Dodecene-1	C ₁₂ H ₂₄	213	— 31	0.7589	1908.9
Tridecene-1	C ₁₃ H ₂₆	102 (10 mm)	— 13	—	2066.4
Tetradecene-1	C ₁₄ H ₂₈	127 (15 mm)	— 12	0.773	2223.8
Hexadecene-1	C ₁₆ H ₃₂	274	+ 4.0	0.7812	2538.7
Octadecene-1	C ₁₈ H ₃₆	179 (15 mm)	+ 18	0.7891	2853.6

The heats of formation of ethene and propene from graphite and molecular hydrogen are —12.6 and —4.7 kcal, respectively. Thus these alkenes are endothermic compounds; the higher alkenes are exothermic.

The alkenes are only slightly soluble in water and the solubility decreases as the number of carbon atoms in the molecule increases. The alkenes dissolve readily in many organic liquids such as alcohol, petroleum ether and benzene.

The molecular refraction of an alkene C_pH_{2p} is greater than p times the refraction equivalent of a CH₂-group (Δ CH₂); the double bond produces an *increment* in the molecular refraction (BRÜHL, EISENLOHR). From measurements carried out by WIBAUT and GELDOLF, this increment is constant in the series of alkenes with a terminal double bond; in calculating the increment, Δ CH₂ is taken as being 4.636. The figures given in Table 29 are for the NaD-line ($\lambda = 5893$) at 20.0°. Slightly different values are found for the increment for the double bond when different homologous series are considered; 1.7 may be taken as the mean value.

The *molecular dispersion*, i.e. the difference in the molecular refraction for the γ - and the α -lines of the hydrogen spectrum ($\lambda = 4341 \text{ \AA}$ and 6563 \AA , respectively), is given in the penultimate column of table 29. The molecular dispersions of these alkenes are greater than those of the corresponding alkanes (last column). EYKMAN has pointed out that the difference between the molecular refraction of an alkene and that of the corresponding alkane, which he denoted as (H₂), has different values depending on the position of the double bond in the carbon chain and on the

groups attached to the double bond. The value of (H_2) is 0.50 ($\lambda = 6563$) for n -alkenes with a terminal double bond compared with the n -alkanes. The application of this principle for determining the position of the double bond is given in 101.

TABLE 29
OPTICAL PROPERTIES OF SOME ALKENES-1

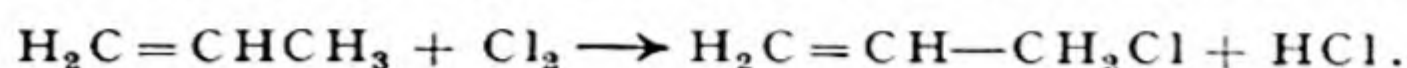
Alkene	$\frac{(n^2 - 1) M}{(n^2 + 2) d}$	Increment	Molecular dispersion	
			Alkene	Alkane
C ₅ Pentene-1	24.86	1.68	0.78	0.62
C ₆ Hexene-1	29.49	1.67	0.89	0.73
C ₇ Heptene-1	34.13	1.68	1.00	0.84
C ₈ Octene-1	38.77	1.68	1.11	0.94
C ₉ Nonene-1	43.41	1.69	1.22	1.05
C ₁₀ Decene-1	48.05	1.69	1.34	—
C ₁₂ Dodecene-1	57.30	1.67	1.55	—
C ₁₆ Hexadecene-1	75.86	1.68	2.00	—
C ₁₈ Octadecene-1	85.13	1.68	2.22	1.84

85. Chemical properties. The most characteristic property of the alkenes is their power of addition. They can combine with a variety of other substances, such as halogens, halogen hydrides or hydrogen; for this reason the alkenes are said to be *unsaturated*. When an unsaturated hydrocarbon is shaken with bromine water, the latter is decolourised because the bromine combines with the alkene. We have here a *reaction on the carbon double bond*. Another reagent which reacts on the double bond is an aqueous solution of potassium permanganate and soda; the unsaturated compound is oxidised by the permanganate, the violet colour disappears and is replaced by brown flocks of hydrated manganese dioxide (BAEYER'S *reaction*). The use of this reaction as a test for the carbon double bond is limited, because various other substances, *e.g.* aldehydes also reduce alkaline permanganate solution.

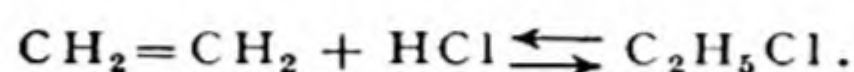
Addition of chlorine or bromine. This addition takes place very easily at ordinary temperatures, *e.g.* by shaking the alkene with bromine water or by treating it with liquid bromine with effective cooling; in some cases carbon tetrachloride, CCl₄, (106) is used as a diluent.

The reaction between chlorine (or bromine) and ethene in the gas phase at 0° is accelerated catalytically by the walls of the vessel in which the reaction is carried out; this effect has been observed in many gas reactions. In the case of ethene and chlorine, the reaction takes place much more rapidly on a glass surface on which a very small amount of water is adsorbed than on a paraffin surface, obtained by carefully covering the inside of the glass reaction vessel with a layer of paraffin (NORRISH). Apparently, the addition is accelerated on a polar surface. It is very noteworthy, that at high temperatures, chlorine (and bromine) reacts with alkenes *by substitution*. When chlorine and excess propene are both separately preheated and

then led together rapidly through a glass tube heated to about 500° , allyl chloride (94) is formed as the main reaction product (GROLL and HEARNE):

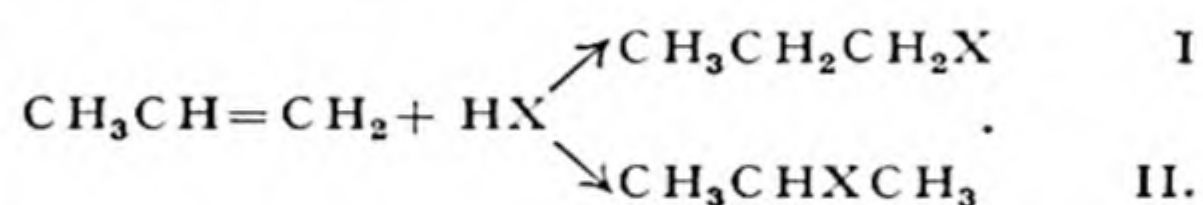


The *addition of hydrogen halide* takes place most rapidly with hydrogen iodide. Hydrogen chloride and hydrogen bromide do not combine with ethene and propene or they react extremely slowly only, unless specific catalysts are used. Thus ethyl chloride is easily formed when ethene and hydrogen chloride gas are passed over bismuth chloride at about 100° . The reaction is reversible:

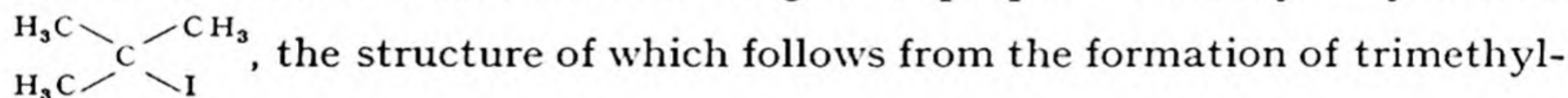


At 500° ethyl chloride is split up quantitatively into ethene and hydrogen chloride. The addition reaction can be carried out at as low a temperature as -78° in the presence of AlCl_3 as a catalyst.

The addition of hydrogen halide to an alkene is exothermic. With propene this addition can take place in two ways:



Experience has shown that the 2-halogenopropane (II) is practically the sole product, along with very small quantities of the 1-halogenopropane (I). A similar course is taken with homologues of propene. Tertiary butyl iodide



carbinol by the action of moist silver oxide, is the sole product from the

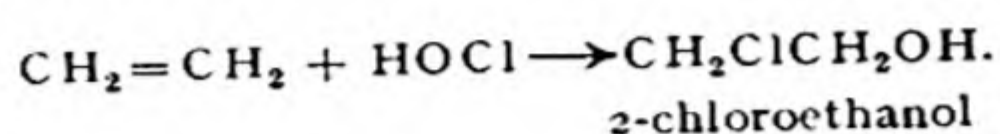
reaction between isobutene $\begin{array}{c} \text{CH}_3 \diagdown \\ \text{C} = \text{CH}_2 \\ \text{CH}_3 \diagup \end{array}$ and hydrogen iodide.

This may be expressed by saying, that in the addition of hydrogen halide, the hydrogen atom becomes attached to the carbon atom of the double bond which carries the most hydrogen atoms (MARKOWNIKOW's rule).

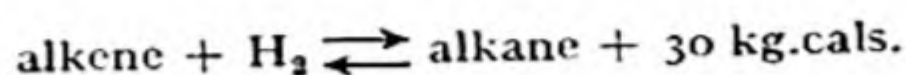
It is noteworthy that the addition of HBr (but not HCl) to propene in the liquid phase is influenced by the presence of small quantities of peroxides. From a mixture of liquid propene and liquid hydrogen bromide in a sealed tube at ordinary temperatures in the absence of oxygen, there is produced exclusively 2-bromopropane by a very slow reaction. If a small quantity of benzoyl peroxide (260) is added to the mixture, however, the reaction product contains 80 % of 1-bromopropane and 20 % of 2-bromopropane.

When liquid hydrogen bromide is allowed to react at room temperatures with liquid vinyl bromide, $\text{CH}_2=\text{CHBr}$, CH_3CHBr_2 is formed in the absence of oxygen; in the presence of peroxide or of oxygen, which in this case can form a small quantity of a peroxide, $\text{CH}_2\text{Br}.\text{CH}_2\text{Br}$ is formed as the main product. This phenomenon, which was discovered by KHARASH, is known as the *peroxide effect*.

The *addition of hypochlorous acid* leads to the formation of chloroalkanols:



The *addition of hydrogen* to alkenes is a reversible reaction:

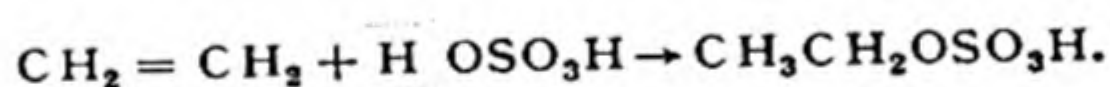


Below 100° the equilibrium lies almost completely on the side of the alkane. The addition of molecular hydrogen to alkenes takes place only in the presence of a catalyst, *e.g.* of finely divided platinum or palladium at ordinary temperatures, or of finely divided nickel at about 150° .

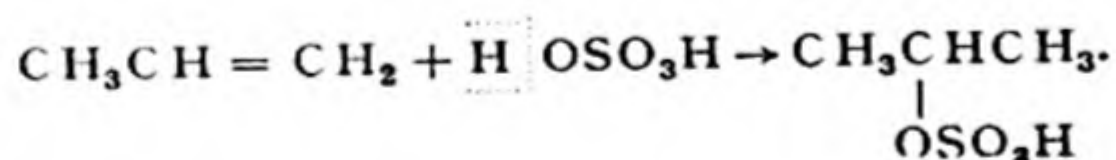
The thermal effect of the addition of a molecule of hydrogen to a molecule of ethene amounts to 32.5 kcal; a value of about 30 kcal. has been found for some homologues.

Amorphous chromium III-oxide, Cr_2O_3 , is a very good dehydrogenation catalyst, by the use of which alkanes break down into alkenes and hydrogen in the temperature range between 350° and 450° without the occurrence of side reactions, so that the equilibrium concentrations (starting from either side) can be determined. At 450° the value of the constant $K_p = \frac{P_{\text{alkene}} \cdot P_{\text{H}_2}}{P_{\text{alkane}}}$ is 5.0×10^{-4} for the ethane-ethene equilibrium and 9.0×10^{-3} for propane-propene (FREY and HUPPKE).

The *addition of sulphuric acid* to alkenes is both of theoretical and practical importance. Ethene reacts with concentrated sulphuric acid at about 80° with the formation of ethylsulphuric acid:



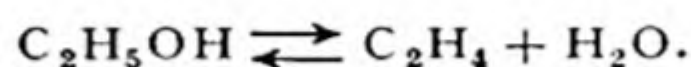
On heating to higher temperatures this substance is broken down again into ethene and sulphuric acid. With homologues of ethene the addition reaction takes place in accordance with MARKOWNIKOW's rule. *Isopropylsulphuric acid* is produced from propene:



This reaction is used in the technical preparation of alcohols. Ethene, which can be isolated from coal-gas (coke-oven gas) or from the mixture of gaseous alkanes produced as a by-product in the thermal decomposition (cracking) of mineral oil distillates (see 26), is absorbed in concentrated sulphuric acid, with the formation of $\text{C}_2\text{H}_5\text{OSO}_3\text{H}$, after which the solution is diluted with water and the alcohol produced by hydrolysis is distilled. BERTHELOT made use of this reaction in 1855 for his synthesis of alcohol from its elements.

In a similar way higher alcohols are obtained from propene and its homologues which occur in considerable quantities in "cracking gases"; in this way secondary or tertiary alcohols are obtained depending on the structure of the alkene used, *e.g.* trimethylcarbinol is produced from isobutene:

Addition of water. Ethene and steam can be made to combine to form ethanol when the mixed gases are passed over certain catalysts such as a mixture of manganese and barium acid phosphates (STANLEY), at 225°. Thus the fission of ethanol into ethene and water, discussed in 80, is reversible:

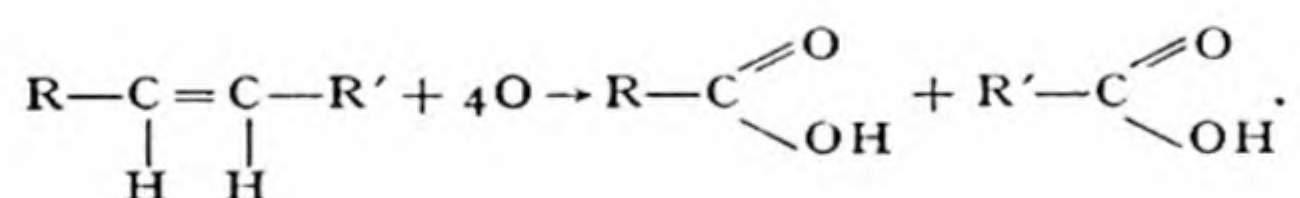


At 225° and a total pressure of one atmosphere, the concentration of the alcohol in the equilibrium mixture is small. The equilibrium constant expressed by the ratio of the partial pressures of the reacting substances, amounts at 225° to

$$K_p = \frac{P_{\text{C}_2\text{H}_5\text{OH}}}{P_{\text{C}_2\text{H}_4} \times P_{\text{H}_2\text{O}}} = 1.07 \times 10^{-2}.$$

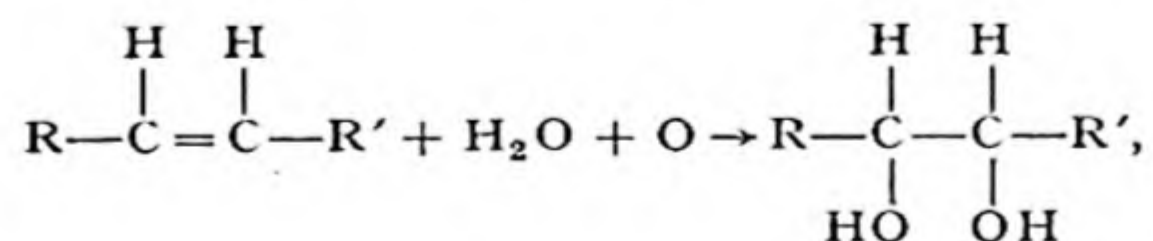
An equilibrium exists also between propene and water with the formation of propanol-2. The catalytic addition of water to ethene is at present used commercially for the preparation of alcohol.

86. Oxidation of alkenes. It has already been mentioned that alkenes are oxidised at ordinary temperatures by a dilute solution of potassium permanganate containing soda; this is a striking difference from the behaviour of the alkanes, which are stable towards oxidising agents at ordinary temperatures. In this way two acids are produced from an alkene according to the equation:



A ketone $\text{R}_1\text{R}_2\text{C}=\text{O}$ and an acid R_3COOH may be produced as oxidation products from an alkene of the structure $\text{R}_1-\text{C}=\text{CH}-\text{R}_3$.

In a number of cases it has been possible to show that the addition of two OH-groups to the double bond is the primary reaction in this oxidation:



with the production therefore of a dihydric alcohol (glycol, see 110); the oxidation then proceeds further on those carbon atoms to which oxygen is already attached (see the general rule on p. 63), so that it eventually

leads to a rupture of the carbon chain between those carbon atoms, which were originally joined by a double bond. From an examination of the acids produced in this oxidation, it is therefore possible to deduce the position of the double bond in the alkene.

Dihydric alcohols can sometimes be prepared by carrying out this oxidation with a very dilute solution of potassium permanganate or with a solution of potassium chlorate in presence of osmium tetroxide. In this way glycol, $\text{CH}_2\text{OHCH}_2\text{OH}$, is produced from ethene.

87. Ozonides. Alkenes may also be oxidised by ozone (HARRIES). Oxygen containing a few percent of ozone is passed through a solution of the alkene in an inert solvent (*e.g.*, CCl_4) at low temperature. In this way there is formed a compound from a molecule of ozone and a molecule of alkene.

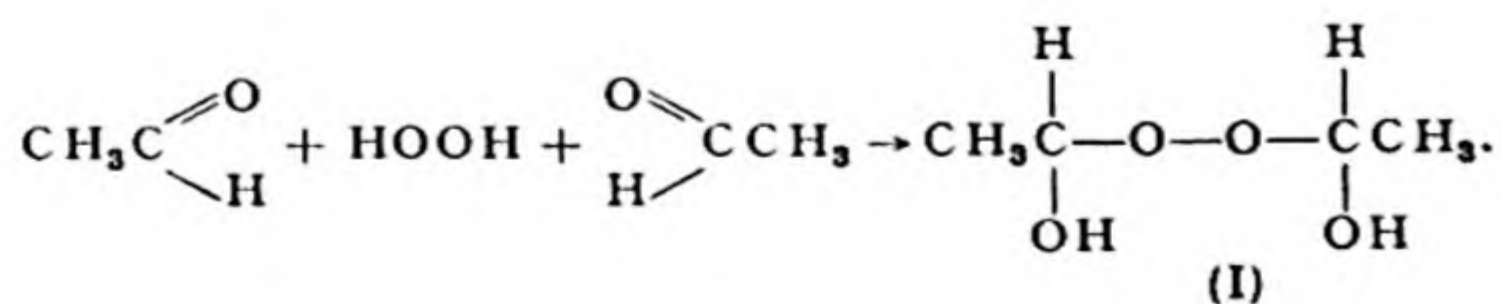
These ozonides, which analysis and determination of the molecular weights show to have the composition $\text{C}_n\text{H}_{2n}\text{O}_3$, are unstable compounds. The lower members of the series may explode violently at ordinary temperatures; the higher members are rather more stable but they still explode on heating.

The ozonides are decomposed on warming with water or with dilute acids, one molecule of ozonide producing two molecules of aldehyde and one molecule of hydrogen peroxide. Experience has shown that by ozonising an alkene and subsequently decomposing the ozonide, the carbon chain of the alkene is broken at the double bond; hence this method may be used for determining the structure of unsaturated carbon chains, since the position of the double bond may be deduced from an examination of the degradation

products so obtained. HARRIES ascribed the structure $\text{R}-\overset{\text{H}}{\underset{\text{O}}{\text{C}}}-\overset{\text{H}}{\underset{\text{O}}{\text{C}}}-\text{R}'$ to the ozonides but more recent investigations of RIECHE have shown that the structure must be represented by the formule $\text{R}-\overset{\text{H}}{\underset{\text{O}}{\text{C}}}-\text{O}-\text{O}-\overset{\text{H}}{\underset{\text{O}}{\text{C}}}-\text{R}'$.

The structure of the ozonide of butene-2 is proved as follows. By the action of hydrogen peroxide on an aldehyde, both dissolved in ether, there is produced a hydroxyalkyl peroxide.

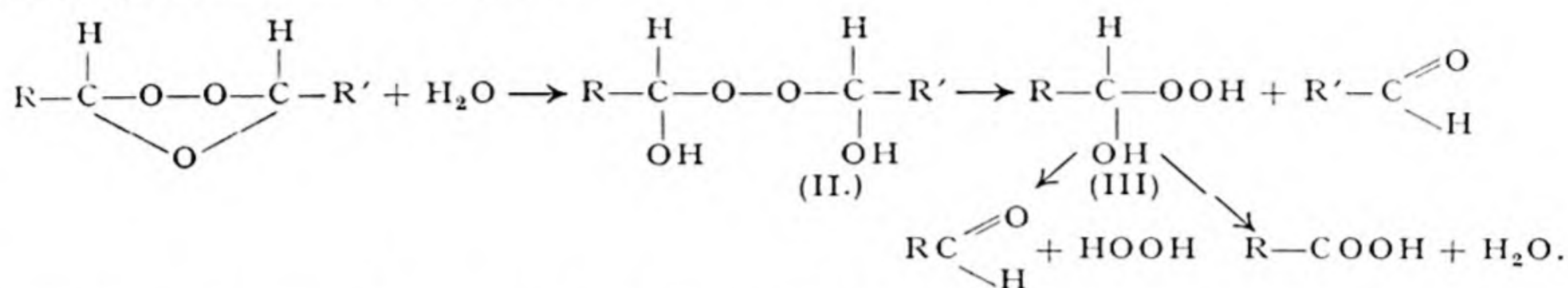
Di-(hydroxyethyl) peroxide (I) is produced from acetaldehyde:



When I is treated in ethereal solution with phosphorus pentoxide, water is removed and a liquid compound is produced to which the annexed structure is ascribed. From its physical properties (density and refractive index) and its chemical behaviour, this compound was identical with the ozonide obtained by ozonising butene-2.



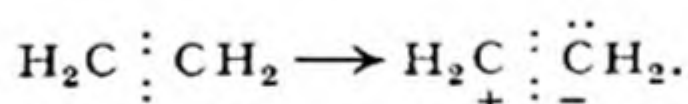
The decomposition of ozonides takes place as follows. As a result of hydrolysis of the ether-like combined oxygen, the primary product is the di-(hydroxyalkyl) peroxide (II), which decomposes into a hydroxyalkyl hydroperoxide (III) and an aldehyde:



Compound III can decompose in two ways, viz. into hydrogen peroxide and aldehyde or into carboxylic acid and water. As a matter of fact, the corresponding carboxylic acids are found in the decomposition products of ozonides as well as the aldehydes and hydrogen peroxide; the di-hydroxyalkyl peroxides can also be isolated in some cases.

From the above, it appears that the double bond is the point of attack in the alkene molecule for addition and oxidation reactions. The carbon double bond is not to be likened to two single bonds, but is a particular kind of bond to which the molecule owes its reactivity.

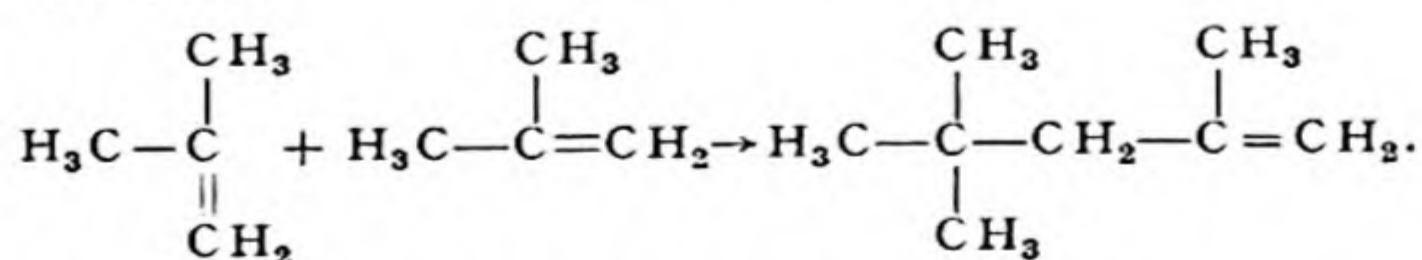
It may be assumed that addition is preceded by a displacement of the electrons of the double bond (polarisation), as a result of which one carbon atom obtains a positive charge and the other a negative charge:



On the addition of HCl for example, the proton will be bound by the lone pair of electrons of the negatively charged carbon atom, while the chlorine ion, which has eight electrons in its outer shell, will combine with the positively charged carbon atom. Addition takes place via an *ionogenic mechanism*.

The *polymerisation of alkenes* to form polymers of high molecular weight is discussed in 103.

Under the influence of sulphuric acid or zinc chloride, the butenes and some of their homologues can be polymerised to dimers and trimers. 2,4,4-Trimethylpentene-1 is formed from *isobutene* by the action of 60 % sulphuric acid at 80°:

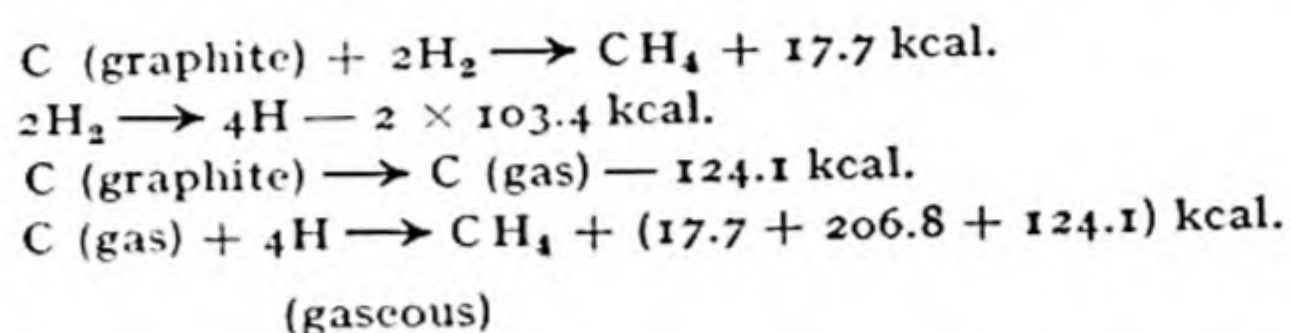


2,4,4-Trimethylpentene-2 is also formed (see 26).

Calculation of bond energies in saturated and unsaturated hydrocarbons

88. A method for calculating energy values for the carbon—carbon and carbon—hydrogen bonds from heats of combustion, was first given by FAJANS; the calculation given below is based on the same principle but is taken from PAULING.

The heat of formation of methane from gaseous carbon atoms and gaseous hydrogen atoms is calculated according to the equations given below:



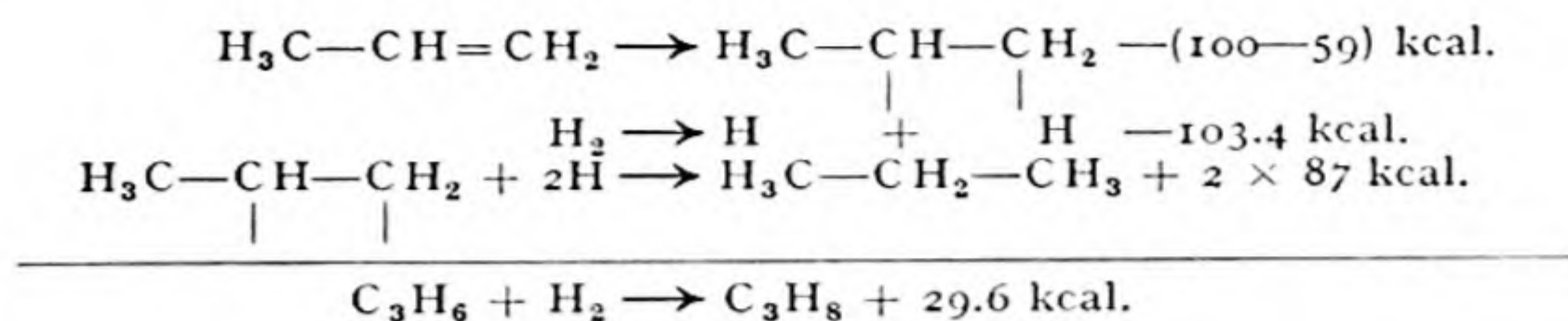
The heat which must be added to convert graphite into gaseous carbon atoms is only known approximately; this heat of sublimation has been derived, for example, from measurements of the vapour pressure of graphite at high temperatures.

The heat of formation of CH_4 from its constituent atoms (348.6 kcal.) calculated in this way, can be considered as being composed of four C—H bonds. Thus the bond energy for a C—H bond amounts to 87 kcal. This is not the energy required by the reaction $\text{CH}_4 \rightarrow \text{CH}_3 + \text{H}$, but is the average of the energy requirements for the reactions, $\text{CH}_4 \rightarrow \text{CH}_3 + \text{H}$; $\text{CH}_3 \rightarrow \text{CH}_2 + \text{H}$; $\text{CH}_2 \rightarrow \text{CH} + \text{H}$; and $\text{CH} \rightarrow \text{C} + \text{H}$.

In a similar way, the heat of formation of C_2H_6 from gaseous atoms is 579 kcal. If $6 \times$ the value for the C—H bond is subtracted from this value, then 57 kcal. is found for the energy of the C—C bond. These calculations can be carried out for the homologues of ethane; in this case it is assumed that all C—H bonds in the alkanes have the same energy value and that the same holds for all the C—C bonds. This assumption is the simplest, because the molecular heats of combustion for the normal alkanes are additive to a very close approximation from the 5th. member of the series upwards and only slight deviations from the additive rule occur with branched chain alkanes. Similar calculations can be carried out for the alkenes and the alkynes, the assumption being made that the bond energies of all the C—H bonds in these molecules are identical with the value for the C—H bond in the alkanes. From the nature of the calculation it follows that the bond energies obtained in this way represent average values and are therefore only approximately correct. PAULING finds the following figures (rounded off to whole calories) for the average values agreeing as closely as possible with experimentally determined heats of combustion:

C—H bond	87 kcal.
C—C „	59 „
C=C „	100 „
C≡C „	123 „

The carbon double bond is therefore stronger than the single bond, but the bond energy of the double bond is smaller than twice the value for the single bond. This is in agreement with the idea that the two bonding forces in a carbon double bond are not identical. The triple bond is stronger than the double bond but is much weaker energetically than three single bonds. As an example for the calculation of the thermal effect of a reaction with the aid of bond energies, the hydrogenation of propene to propane may be considered and the reaction may be imagined as being split up into various steps.



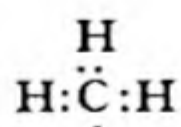
KISTIAKOWSKY has accurately measured the heat evolved in the catalytic hydrogenation of alkenes and from this determined the heat of hydrogenation for various alkenes. According to these measurements the heat of hydrogenation in kcal. per gram-molecule amounts to 32.6 for ethene, 30.1 for propene and 28.4 for *isobutene*. A more accurate agreement with the number calculated from bond energies is not to be expected because the latter are average values.

The free alkyl groups methyl and ethyl

89. In the first half of the previous century repeated attempts were made, for example by FRANKLAND, to prepare hydrocarbons of the composition $\text{C}_n\text{H}_{2n+1}$, *e.g.*, by extracting the iodine from methyl iodide. In all these cases, however, instead of the expected compound CH_3 (methyl), there was produced a substance with double the molecular weight, ethane, which was formed apparently by combination of two free methyl groups (compare the WURTZ method for making alkanes **17**).

In 1929 PANETH showed that the methyl group could exist in the free state, (compare **17**). Gaseous hydrogen mixed with the vapour of tetramethyllead, $\text{Pb}(\text{CH}_3)_4$ was passed at a high velocity and very low pressure through a quartz tube. When the tube was heated at one point, the tetramethyllead decomposed and deposited a very thin layer of lead as a lead mirror on the wall of the tube. Now when the heated part of the tube was allowed to cool while the gas stream was still passing and the tube was heated at another spot about 10 cm in front of the lead mirror, a second lead mirror was deposited where the tube was now heated, but the lead mirror in the cooler part of the tube disappeared. The explanation of this is as follows: in the decomposition of tetramethyllead, methyl groups (free radicals) are produced, which are carried forward by the gas stream and meet the cool lead mirror before they have had time to combine with one another to form ethane, C_2H_6 . The very reactive and unstable substance, *methyl*, then combines with the lead to re-form volatile tetramethyllead. It appears from calculation that the life of free methyl is extremely short, for the concentration of this substance was reduced to a half after about 0.006 second. Hence the experiment succeeds only when the gas mixture is passed through the tube at very low pressures and high velocities. PANETH was also able to remove a zinc mirror in the same way; dimethylzinc was then formed and could actually be isolated. In a similar way PANETH demonstrated the existence of free *ethyl* (by decomposing tetraethyllead), which also has a very short life.

The methyl molecule has an *odd* number of valency electrons. The outer shell of the carbon atom contains three pairs of electrons and one uncombined or unshared electron:



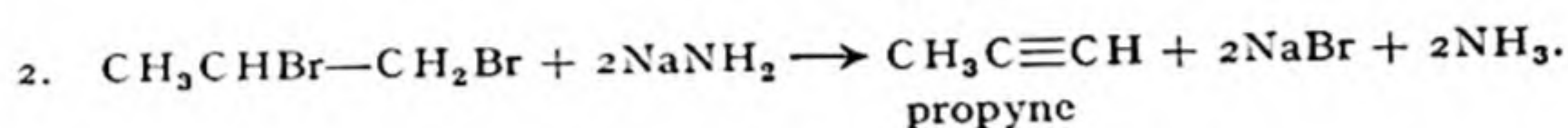
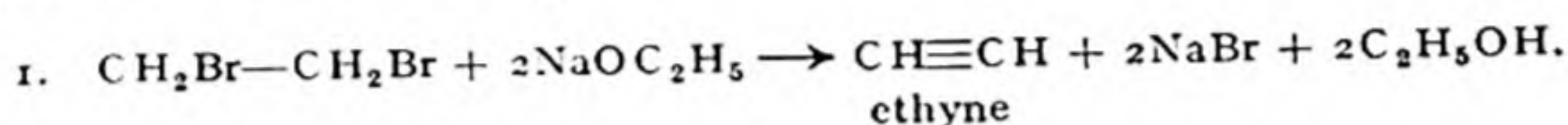
This unshared electron tries to form a pair of electrons with a valency electron of another atom; consequently methyl is a very reactive and very unstable compound.

The very unstable radical $>\text{CH}_2$, *methylene*, is produced by the thermal decomposition of diazomethane (**210**).

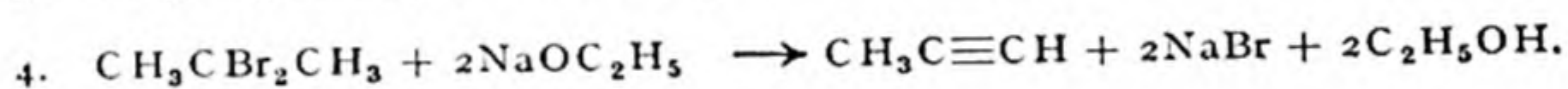
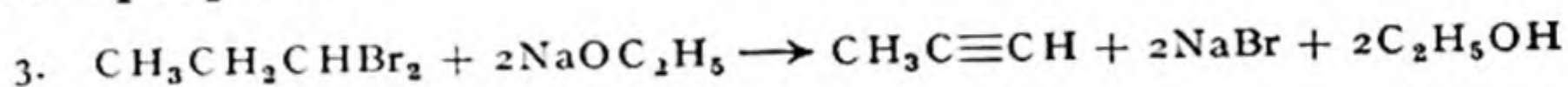
(b) *Hydrocarbons with a triple bond (alkynes)*

90. These hydrocarbons contain four atoms of hydrogen less than the alkanes with the same number of carbon atoms; the general formula is C_nH_{2n-2} . The names of these compounds are formed by replacing the suffix *ane* in the name of the corresponding saturated hydrocarbon, by *yne*; C_2H_2 *ethyne*, C_3H_4 *propyne*, C_4H_6 *butyne*; the general name is *alkyne*.

Methods of formation and properties. The alkynes can be prepared by extracting two molecules of hydrogen halide from dihalogenoalkanes. This reaction may be carried out by heating with alcoholic caustic soda or by the action of sodamide, *e.g.*:



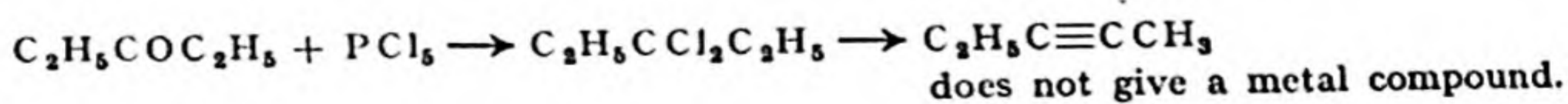
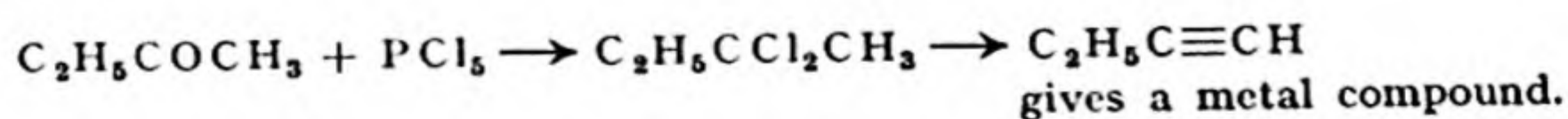
Propyne can be obtained both from 1,1-dibromopropane and from 2,2-dibromopropane:



It is apparent from examples 3 and 4 that the fission of two molecules of hydrogen bromide occurs between two adjacent carbon atoms. Hence the course of the reaction is similar to that involving the formation of alkenes from alkyl halides. The alkynes can combine with two molecules of hydrogen, halogen or hydrogen halide. The presence of a triple bond is assumed in the alkynes for reasons similar to those put forward for supposing that there is a double bond in the alkenes.

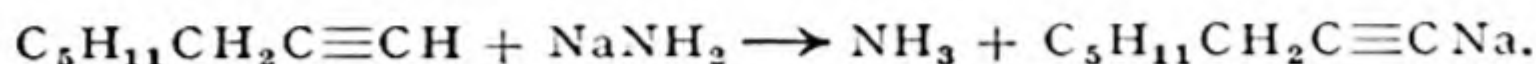
In ethyne both of the hydrogen atoms may be replaced by certain metals; it reacts with an ammoniacal solution of cuprous chloride with the formation of a reddish brown precipitate of the composition Cu_2C_2 . This is a sensitive reaction for acetylene. With an ammoniacal solution of silver nitrate a colourless precipitate of Ag_2C_2 is produced; these metal compounds are decomposed by dilute acids with the re-formation of ethyne. Propyne and those homologues in which the group $-C\equiv CH$ occurs, can also form metal compounds.

Example:

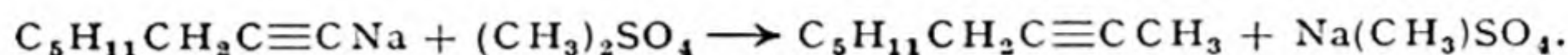


The silver compounds of the alkynes, and to a lesser extent the cuprous compounds, are explosive. The hydrogen atom of the group $\equiv\text{C}-\text{H}$ can also be replaced by alkali metals; on heating sodium and acetylene the compounds $\text{HC}\equiv\text{CNa}$ and $\text{NaC}\equiv\text{CNa}$ are produced. These substances are decomposed by water with the re-formation of acetylene.

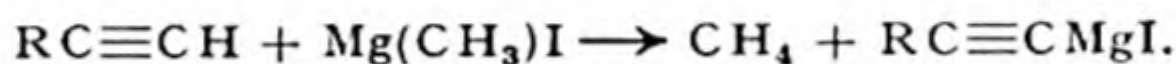
These sodium compounds can also be produced by the action of sodamide on the alkynes in liquid ammonia:



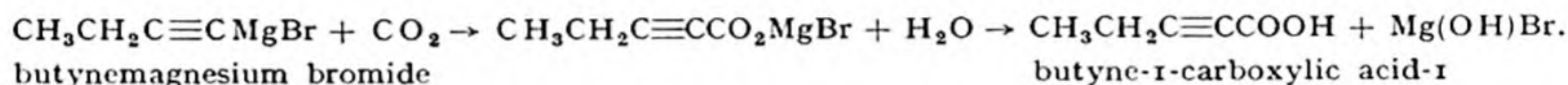
By the action of dimethyl sulphate the sodium atom can be replaced by the CH_3 group:



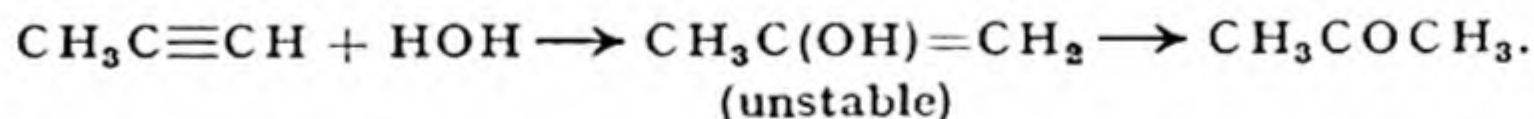
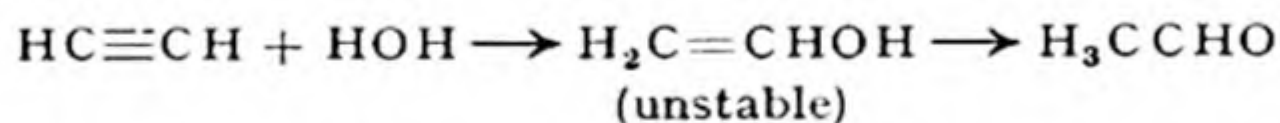
Alkynes containing the group $-\text{C}\equiv\text{CH}$, react with an ethereal solution of methylmagnesium iodide; in this reaction methane is formed and a magnesium derivative of the alkyne, which separates as a solid:



These alkynemagnesium halides can be used for syntheses, *e.g.*:



Another property of the alkynes is, that they can combine with a molecule of water when treated with dilute acids in the presence of mercury salts which act catalytically. In this way acetaldehyde is produced from ethyne, and acetone from propyne. Probably an unsaturated alcohol, which is unstable (see 95) and passes over into aldehyde (or ketone), is formed as an intermediate product:



The catalytic action of mercury salts in this reaction depends on the formation of complex mercury compounds. For example, if propyne is passed into a solution of mercuric chloride, a precipitate is produced of the composition $3\text{HgCl}_2 \cdot 3\text{HgO} \cdot \text{C}_3\text{H}_4$, from which acetone is formed by the addition of hydrochloric acid.

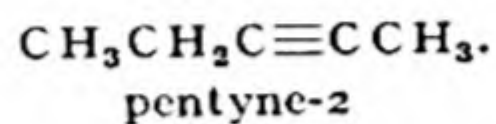
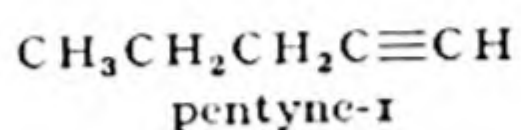
In the catalytic reduction of ethyne, ethene is the primary product, which is then reduced further to ethane.

With higher alkynes, *e.g.* with $\text{H}_3\text{CC}\equiv\text{CC}_2\text{H}_5$, $\text{C}_2\text{H}_5\text{C}\equiv\text{CC}_2\text{H}_5$, etc., the catalytic reduction can be carried out in the liquid phase by using colloidal palladium or finely divided nickel, in such a way that the corresponding alkene is obtained in good yield; in this case the *cis*-form is produced (BOURGUEL; DUPONT; CAMPBELL).

From measurements by KISTIAKOWSKY it follows that the thermal effect for the addition of molecule of hydrogen to ethyne amounts to 42.5 kcal.

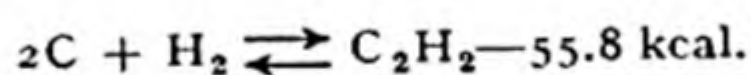
The alkynes can be caused to polymerise in various ways depending on the reaction conditions. When acetylene is passed through a red hot tube (temperature about 700°) three molecules combine together to give benzene (213). Under the same conditions homologues of benzene are formed from homologous alkynes (see also 91 and 216 for the polymerisation of ethyne).

By heating with potassium alcoholate the higher alkynes can be converted into isomers in which the triple bond takes up a different position in the molecule (FAWORSKY):



91. *Ethyne (acetylene)* is a colourless gas possessing a faint ethereal odour when pure; it is slightly soluble in water, more soluble in alcohol and readily soluble in acetone. The critical temperature is 35.5° and the critical pressure 61.6 atm. Acetylene burns with a highly luminous, sooty flame. Mixtures of acetylene and air are very explosive between wide limits of composition (explosion limits) varying between about 5 and 70 % of acetylene. The melting point of acetylene is -81.8° and the sublimation point of the solid -83.6° (760 mm).

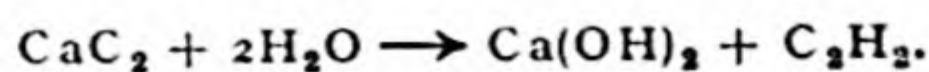
Acetylene is formed by direct synthesis from its elements in an electric arc between carbon electrodes in an atmosphere of hydrogen (BERTHELOT 1863). From the heat of combustion of acetylene (313 kcals) it follows that the heat of formation from gaseous hydrogen and solid carbon amounts to -55.8 kcal (see 114):



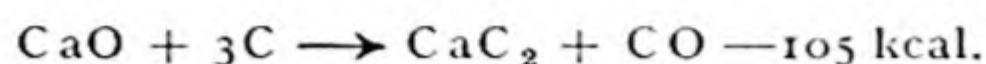
The reaction is reversible; from the LE CHATELIER—VAN 'T HOFF principle it follows that an appreciable quantity of acetylene can be formed from its elements only at very high temperatures; about 3 % is found at 2500° . Hence it is to be expected that acetylene will be unstable at temperatures below 1000° , *i.e.* it will show a tendency to decompose into carbon and hydrogen. Actually this decomposition can occur in compressed acetylene gas and the reaction may take place explosively due to the heat set free.

Ethyne can be produced by the thermal decomposition of alkanes (occurrence of small quantities of acetylene in coal-gas). When methane is passed at a very high velocity over tungsten wires heated to about 2000° , the exit gas contains a few per cent. of acetylene; CH groups are produced by the decomposition of the methane and they combine with one another to form acetylene molecules at lower temperatures.

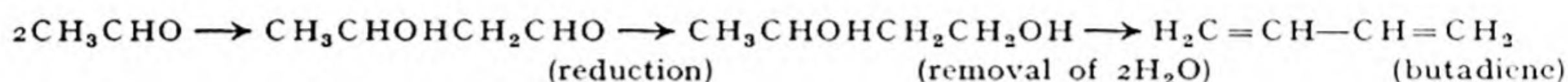
Acetylene is obtained on a commercial scale by treating *calcium carbide* with water:



Calcium carbide, which may be considered as the calcium derivative of ethyne, is prepared by heating carbon (coke) with CaO (quicklime) in an electric furnace to about 2000° ; this reaction also is reversible and strongly endothermic:



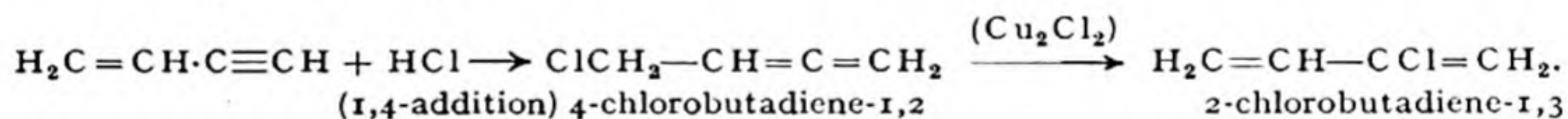
Acetylene is an important starting material for the organic chemical industry. Acetaldehyde is prepared by passing acetylene through warm, dilute sulphuric acid containing mercuric sulphate in solution. The acetaldehyde is then oxidised with atmospheric oxygen with or without manganese acetate as a catalyst, to acetic acid. Acetaldehyde itself is used for the technical synthesis of butadiene:



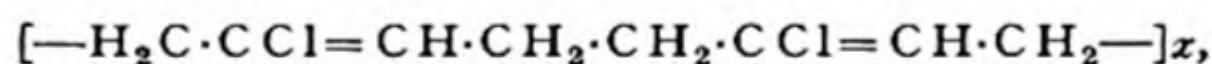
Butadiene is used for the synthesis of artificial rubber. Several important starting materials for the manufacture of artificial resins are made from acetylene, for example, vinyl chloride (94) and vinyl acetate (95). NIEUWLAND found that when acetylene is passed through an aqueous solution of cuprous chloride and ammonium chloride it is converted into a dimer, *vinylacetylene* (b.p. $+5^{\circ}$):



n-Butane is obtained from vinylacetylene by catalytic reduction; one hydrogen atom in vinylacetylene is replaceable by an atom of silver. This settles the structure. When vinylacetylene is shaken with hydrochloric acid, 4-chlorobutadiene-1,2 is produced and this is converted by the catalytic influence of cuprous chloride into 2-chlorobutadiene-1,3 or chloroprene:



Chloroprene can be converted into a polymer:



which resembles caoutchouc in many respects and is prepared on a large scale under the name of *Duprene* or *Neoprene* (CAROTHERS).

Acetylene is introduced into commerce in steel cylinders containing acetone and kieselguhr into which acetylene is compressed to a pressure of 12 atm. At this pressure one volume of acetone dissolves about 300 volumes of the hydrocarbon. In special cases acetylene is used for lighting purposes (floating lights, etc.), and it finds an important application in the oxyacetylene-flame (temperature about $3,500^{\circ}$) for the welding of steel billets or plates.

(c) *Hydrocarbons with two double bonds (Alkadienes)*

92. These hydrocarbons have the same general formula $\text{C}_n\text{H}_{2n-2}$ as the alkynes with which they are therefore isomeric. They are denoted by the suffix *diene*; the simplest compound of this series is propadiene or allene, $\text{H}_2\text{C}=\text{C}=\text{CH}_2$. This compound is produced by the action of zinc on 1,2-dibro-

mopropene-2, $\text{H}_2\text{C}=\text{CBrCH}_2\text{Br}$, by which two bromine atoms are removed. Allene is a gas at ordinary temperature, b.p. -32° ; m.p. -146° .

Stereostructure of allene derivatives (compare 291). In the space model of propadiene the valence forces of the two double bonds lie in planes at right angles to one another, so that two mirror image forms can occur for compounds of the type $\begin{matrix} \text{A} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{B} \end{matrix} = \text{C} = \text{C} = \begin{matrix} \text{A} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{B} \end{matrix}$, as already mentioned by VAN 'T HOFF.

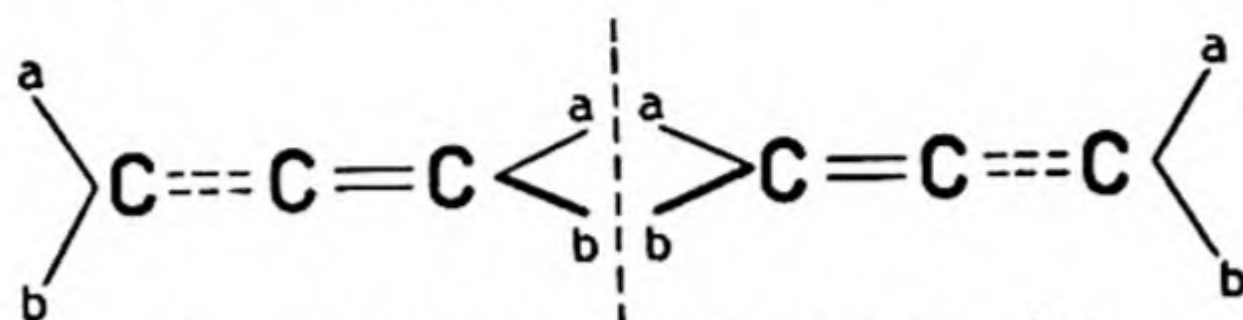


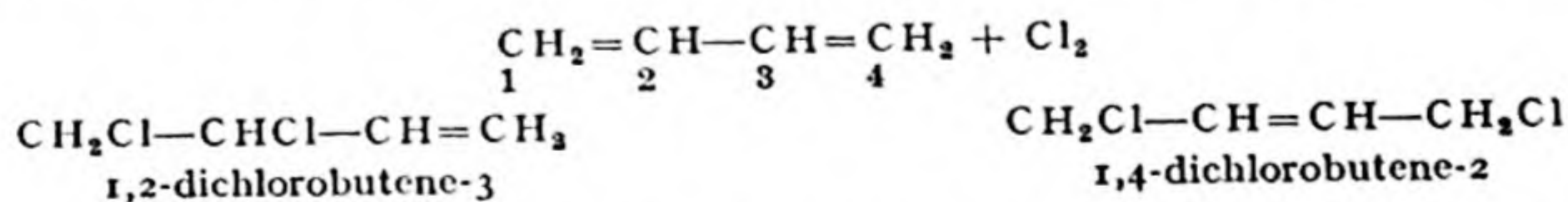
Fig. 28. Space model of propadiene

We are dealing here with a molecule which contains no asymmetric carbon atom, but in which the elements of symmetry mentioned in 37 are wanting. MAITLAND and MILLS have found an example of this. They prepared the *dl*-form of 1,3-diphenyl-

1,3-dinaphthylpropenol, $\begin{matrix} \text{C}_{10}\text{H}_7 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{C}_6\text{H}_5 \end{matrix} = \text{CH} - \begin{matrix} \text{C}_6\text{H}_5 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{C}_{10}\text{H}_7 \end{matrix}$ from which *d*-diphenyldinaphthylallene

$\begin{matrix} \text{C}_6\text{H}_5 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{C}_{10}\text{H}_7 \end{matrix} = \text{C} = \text{C} = \begin{matrix} \text{C}_6\text{H}_5 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{C}_{10}\text{H}_7 \end{matrix}$, was produced by warming with a little *d*-camphorsulphonic acid; the allene derivative showed a specific rotation of $+437^\circ$. When the removal of water from the alcohol mentioned above was carried out by means of *l*-camphor sulphonic acid the optical antipode of the above mentioned allene derivative with a specific rotation of -438° , was produced. The camphorsulphonic acid acts catalytically in the removal of water; probably an ester is formed as an intermediate, which decomposes on warming into camphorsulphonic acid and the allene derivative; the reaction takes an asymmetric course (compare 209) under the influence of an optically active catalyst (*d*- or *l*-camphorsulphonic acid).

Butadiene-1,3 (divinyl or erythrene) $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$, can be prepared by splitting off two molecules of hydrogen chloride from 1,4-dichlorobutane, $\text{CH}_2\text{ClCH}_2\text{CH}_2\text{CH}_2\text{Cl}$. This butadiene (b.p. $+1^\circ$), is the simplest example of a hydrocarbon with *conjugated double bonds*. By this term is meant the grouping $>\text{C}=\text{C}-\text{C}=\text{C}<$. In compounds in which this grouping occurs, addition of two mono-valent atoms (or groups of atoms) is frequently observed to take a peculiar course. Thus by the action of chlorine (1 mol.) on 1,3-butadiene, a mixture of two isomeric dichlorobutenes is produced:



The position of the double bond in these isomers is proved by oxidation; 1,2-dichloropropionic acid is produced from 1,2-dichlorobutene-3 and monochloroacetic acid from 1,4-dichlorobutene-2. 1,4-Dichlorobutene is

formed therefore by the addition of chlorine atoms to carbon atoms 1 and 4, while a double bond is produced between carbon atoms 2 and 3.

This course of addition to a conjugated system of double bonds, which was discovered by THIELE, is known as 1,4-addition. Many cases of 1,4-addition to a conjugated system of double bonds have been observed, especially with more complicated compounds.

The molecular refraction of hydrocarbons, in which conjugated double bonds occur, is greater than would be expected on the basis of the presence of two double bonds; this increase in the molecular refraction is called the *exaltation* of the conjugated system.

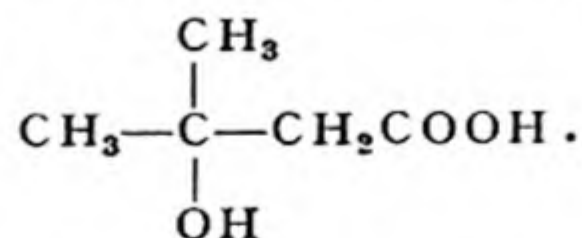
The molecular refraction of hexadiene-2,4, $\text{H}_3\text{C}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_3$, is 30.64. By calculation from the refraction equivalents for carbon, hydrogen and for two double bonds, it should be: $(6 \times 2.55) + (10 \times 1.04) + (2 \times 1.676) = 29.05$. Hence the exaltation of the molecular refraction is 1.59. The molecular refraction for hexadiene-1,4 ($\text{H}_2\text{C}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_3$) is 29.3 and for hexadiene-1,5 ($\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}_2$) it is 29.07. These hexadienes in which the double bonds are not conjugated, show no exaltation.

Butadiene is an important starting material for the preparation of artificial rubber; for a technical synthesis see 302.

93. Another important hydrocarbon of this series is *2-methylbutadiene-1,3* or *isoprene*, C_5H_8 or $\text{CH}_2=\underset{\text{CH}_3}{\text{C}}-\text{CH}=\text{CH}_2$. This hydrocarbon is closely related

to caoutchouc (300) and natural rubber; the atom grouping of isoprene is also met with in the molecular structure of a number of terpenes (compare also 95). Isoprene (b.p. 33.7°) can be prepared by allowing limonene (297) vapour to impinge on a red hot platinum wire.

The structure of isoprene is apparent from the following. By the addition of two molecules of hydrogen bromide to isoprene and to 3-methylbutadiene-1,2 (dimethylallene) $(\text{CH}_3)_2\text{C}=\text{C}=\text{CH}_2$, there is produced the same dibromopentane, viz. 3-methyl-1,3-dibromobutane, $(\text{CH}_3)_2\text{CBr}.\text{CH}_2.\text{CH}_2\text{Br}$, the structure of which is proved by its conversion into 2-hydroxy-2-methylpropane carboxylic acid (2-hydroxyvaleric acid)



The structure of dimethylallene follows from the synthesis described below.

2-Methylbutanol-2, $\text{CH}_3-\underset{\text{OH}}{\overset{\text{CH}_3}{\text{C}}}-\text{CH}_2\text{CH}_3$ and 3-methylbutanol-2, $\text{CH}_3-\underset{\text{CH}_3}{\text{CH}}-\text{CHOH}-\text{CH}_3$,

prepared as described in 59, are converted into the corresponding iodides, from which hydrogen iodide is subsequently removed. In each case there is produced 2-methylbutene-2 (trimethylethene), $(\text{CH}_3)_2\text{C}=\text{CHCH}_3$; any other position for the double bond is excluded by the method of formation from the two iodides. Trimethylethene

adds on two atoms of bromine with the production of 2-methyl-2,3-dibromobutane, $(\text{CH}_3)_2\text{CBrCHBrCH}_3$.

On treating this compound with alcoholic potash, two molecules of hydrogen bromide are split off and 3-methylbutadiene-1,2, $(\text{CH}_3)_2\text{C}=\text{C}=\text{CH}_2$, is formed.

This structure is confirmed by the production of propanone by oxidising 3-methylbutadiene-1,2.

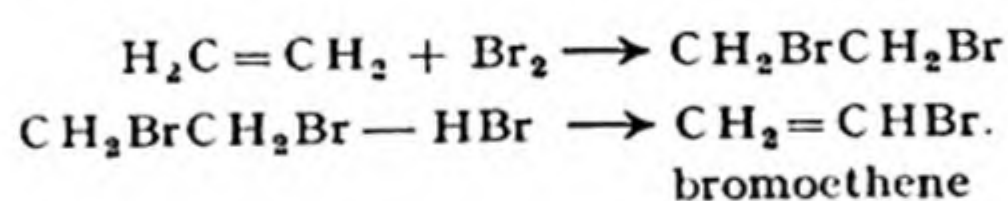
(xi) SUBSTITUTION PRODUCTS OF UNSATURATED HYDROCARBONS

(a) Unsaturated halogeno-compounds

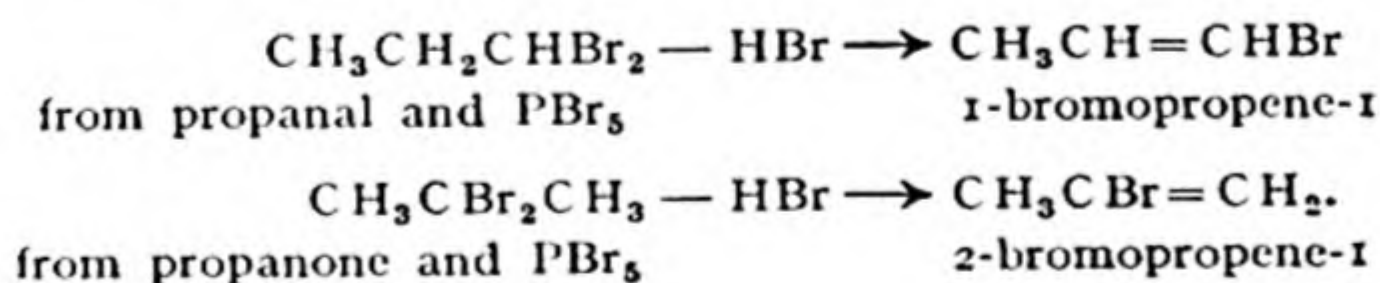
94. Unsaturated halogeno-compounds, unsaturated alcohols, unsaturated acids, etc. may be considered as substitution products of the alkenes, in which a hydrogen atom is replaced by halogen, OH, COOH, etc., respectively. Thus in these compounds two characteristic features appear: 1 the double bond and 2 the substituent.

In general the properties of the second characteristic group are modified by the presence of a double bond. The effect of the double bond depends on the position which the second group occupies in the molecule with respect to the double bond.

As the first example, the different types of unsaturated halogeno-compounds will be considered. These can be prepared by adding halogen to the alkene and removing a molecule of hydrogen halide from the alkene dihalide so obtained, by warming with alcoholic potash:



Halogenoalkenes of this type can also be obtained by removing a molecule of hydrogen halide from a dihalogenoalkane, in which both halogen atoms are combined on one carbon atom:



In these compounds the bromine atom is attached directly to the doubly bound carbon atom, as appears from the method of formation. Experience has shown that the halogen atom in these and similar compounds, is very slightly reactive compared with the halogen atom in halogenoalkanes. *In compounds of the type $\text{RCH}=\text{CHX}$ or $\text{RCX}=\text{CHR}'$ the halogen atom does not take part in double decomposition, or more accurately, replacement reactions.*

Unsaturated alcohols are not formed by the action of alkali; neither are

unsaturated ethers produced by the action of sodium alcoholate or unsaturated amines by the action of ammonia.

The only reaction which does take place with these reagents, is the removal of a molecule of hydrogen halide to produce a hydrocarbon of the formula C_nH_{2n-2} .

Besides 1-bromopropene-1 and 2-bromopropene-1 a third bromopropene, 1-bromopropene-2 or *allyl bromide*, is known to which the structural formula $CH_2=CHCH_2Br$ must be ascribed, because only three isomeric substitution products of propene are possible, in which one hydrogen atom has been replaced by bromine and the structure of the two other bromopropenes follows from their methods of preparation.

The bromine atom in 1-bromopropene-2 will undergo double decomposition in the same way as the bromine atom in an alkyl bromide.

This 1-bromopropene-2 is produced by the action of PBr_3 on the unsaturated alcohol $CH_2=CHCH_2OH$, *propene-2-ol-1* or *allyl alcohol* (see 95).

In a halogenoalkene, in which the halogen atom is attached to a singly bound carbon atom, the halogen atom is reactive like a halogen atom in an alkyl halide. The double bond has an effect on the reactivity of a halogen atom then only if this halogen atom is attached to a doubly bound carbon atom. Conversely, from the ability or otherwise of a halogen atom in a compound $C_nH_{2n-1}X$ to undergo double decomposition, it may be concluded whether this halogen atom is attached to a singly bound or a doubly bound carbon atom.

Chloroethene or *vinyl chloride*, $CH_2=CHCl$, b.p. -12° and *bromoethene* or *vinyl bromide*, $CH_2=CHBr$, b.p. 15.8° , easily pass over into polymeric compounds, which must be attributed to the presence of the double bond (see 103).

1-Chloro-(bromo- or iodo-)propene-2, *allyl chloride*, *allyl bromide* and *allyl iodide*, boiling at 46° , 70° and 102° respectively, are employed in syntheses where it is desired to introduce the allyl group, $CH_2=CH-CH_2-$.

1-Chloropropyne-2 or *propargyl chloride*, $HC\equiv CCH_2Cl$, (b.p. 65°), which can be prepared from propargyl alcohol, $HC\equiv CCH_2OH$ (see 96) and PCl_5 , is an example of a halogeno-compound of the type $C_nH_{2n-3}X$. Propargyl chloride can form metal derivatives ($\equiv CH$ group) and the chlorine atom can be replaced by mono-valent groups of atoms, which is in agreement with the structural formula.

Dichloroethyne or *dichloroacetylene*, $ClC\equiv CCl$ (b.p. 33°) is produced by passing acetylene into a solution of $KOCl$ containing an excess of potassium hydroxide. Dichloroacetylene is a very unstable compound which explodes violently in contact with air.

(b) *Unsaturated alcohols (alkenols)*, $C_nH_{2n}O$

95. The simplest representative of this series is *propene-2-ol-1* or *allyl alcohol* $CH_2=CHCH_2OH$, which can be prepared by methods described later (see 122). Propanol-1 is produced from allyl alcohol by catalytic reduction. From this it follows that the group CH_2OH occurs in allyl alcohol, which is confirmed by the products obtained on oxidation. Allyl alcohol can be oxidised to an unsaturated aldehyde, *propenal* (*acrolein*), from which *ethene carboxylic acid* or *acrylic acid* is produced by careful oxidation:

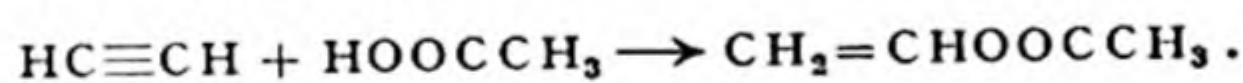


Allyl alcohol can add on two atoms of halogen; for the addition of two OH-groups see 86.

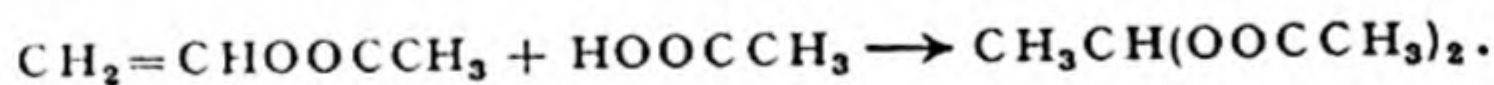
The hydroxyl group in allyl alcohol is attached to a singly bound carbon atom. Aliphatic alcohols in which the hydroxyl group is attached to a doubly bound carbon atom, are not stable (ERLENMEYER's rule); in those cases in which the occurrence of such unsaturated alcohols might be expected, isomeric compounds are obtained.

On splitting off a molecule of water from glycol, $HOCH_2CH_2OH$, ethenol, $CH_2=CHOH$ is not produced but the isomeric ethanal, CH_3CHO . *Ethenol* or *vinyl alcohol* is unknown in the free state; derivatives of this compound like vinyl chloride or bromide already mentioned, are well known.

Vinyl acetate, $CH_2=CHOOCCCH_3$, is prepared by the action of acetylene on acetic acid in presence of a mercury salt as catalyst.



By the further action of acetic acid, *ethylidene diacetate* is produced.



Vinyl acetate is readily converted into polymeric products, which are used for the manufacture of synthetic resins (see 103).

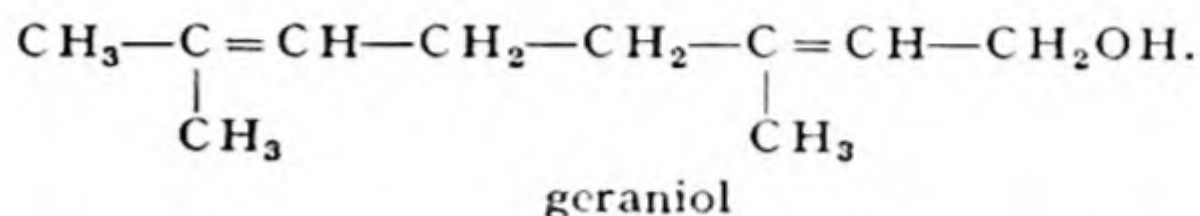
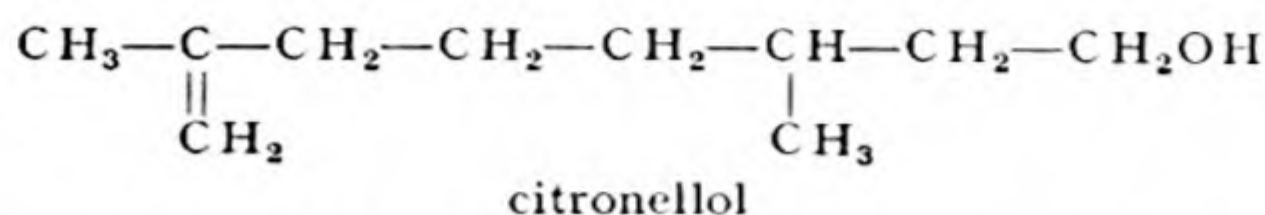
Later on we shall learn about compounds in which the grouping $\begin{array}{c} OHH \\ | \quad | \\ -C=C- \end{array}$ occurs (see 149).

Allyl alcohol (b.p. 97.06° , m.p. -50°) is miscible with water in all proportions.

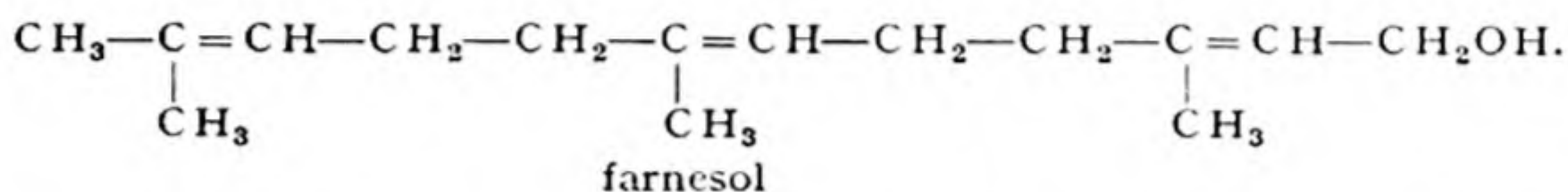
A derivative of allyl alcohol, *diallyl disulphide* $CH_2=CHCH_2S-SCH_2CH=CH_2$, is the chief constituent of oil of garlick and has its characteristic odour. The name allyl alcohol is derived from the botanical name for garlick, *allium sativum*. Diallyl disulphide is prepared synthetically by the action of allyl bromide on sodium disulphide.

Unsaturated alcohols with one or more double bonds occur as components of essential oils (212, 294); some of these, such as *citronellol*, $C_{10}H_{20}O$, boiling at 225° and *geraniol*,

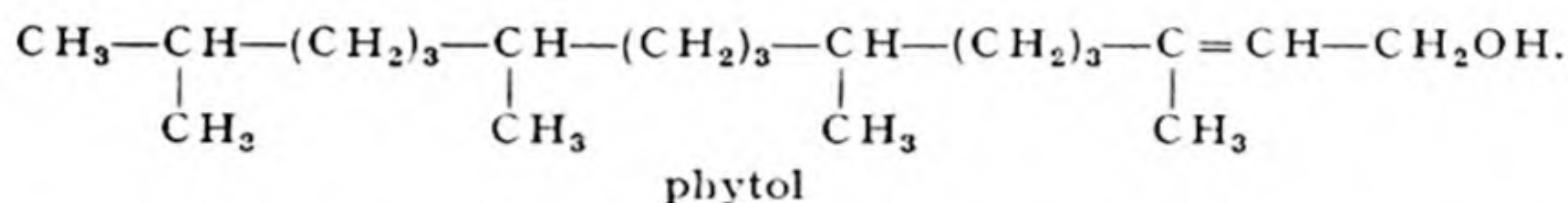
$C_{10}H_{18}O$, boiling at 230° find application in the perfumery industry. Both alcohols have an odour like roses and occur, for example, in oil of roses and in geranium oil:



Farnesol, $C_{15}H_{26}O$, b.p. 160° at 10 mms., smells like lily of the valley:



To this group also belongs *phytol*, $C_{20}H_{40}O$, b.p. 145° at 0.03 mm., which is obtained as a fission product from chlorophyll (321):



When the structures of these alcohols are compared, it appears that the carbon skeleton of isoprene (93) is repeated in the carbon chain, twice in citronellol and geraniol, three times in farnesol and four times in phytol.

96. *Propyne-2-ol-1* (*propargyl alcohol*) $\text{CH}\equiv\text{CCH}_2\text{OH}$, is an alcohol with a triple bond, which can be obtained in the following way: $\text{CH}_2\text{BrCHBrCH}_2\text{Br}$, 1,2,3-tri-bromopropane, on treatment with potash gives 1,2-dibromopropene-2, $\text{CH}_2:\text{CBrCH}_2\text{Br}$, from which 2-bromopropene-2-ol-1, $\text{CH}_2:\text{CBrCH}_2\text{OH}$, is produced by the action of potassium acetate and subsequent hydrolysis, since only the terminal bromine atom here is amenable to double decomposition (94). When this alcohol is warmed again with potash, a further molecule of hydrogen bromide is split off and propyne-2-ol-1 or propargyl alcohol is obtained. The structure of the substance is apparent both from its method of formation and from its properties; it gives metal derivatives ($\equiv\text{CH}$ group) and as a primary alcohol it may be oxidised to an acid, ethyne carboxylic acid or propiolic acid, $\text{HC}\equiv\text{CCOOH}$, with the same number of carbon atoms.

Propargyl alcohol is a pleasant smelling liquid, soluble in water, boiling at $114-115^\circ$ and having a spec. grav. of 0.963 at 21° . The metal derivatives of this substance are explosive.

(c) *Unsaturated aldehydes and ketones*

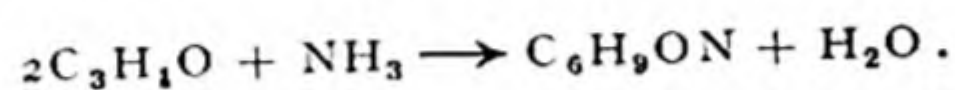
97. The simplest unsaturated aldehyde is *propenal* or *acrolein*, $\text{CH}_2=\text{CHCHO}$. This compound can be obtained by heating glycerol with potassium bisulphate, which splits off a molecule of water. Acrolein is a liquid, b.p. 52.4° , setting point -87° and $d_4^{15} = 0.8447$. It possesses a very intense, intolerable odour from which the name (*acer* = acrid of sharp, *oleum* = oil) is derived;

acrolein is produced is small amount in the thermal decomposition of fats.

By reduction, propenal is converted into *2-propenol-1* and under more powerful conditions into propanol-1. On careful oxidation, propenal is converted into ethene carboxylic acid (acrylic acid).

Acrolein polymerises very easily giving an odourless, solid mass of *disacryl*, which cannot be reconverted into acrolein. The polymerisation of acrolein can be greatly retarded by adding small quantities of polyhydric phenols, *e.g.* quinol or pyrogallol (MOUREU).

The action of ammonia on propenal takes a different course from that with saturated aldehydes, viz. according to the equation:



This *propenal-ammonia* is an amorphous, basic substance, readily soluble in water.

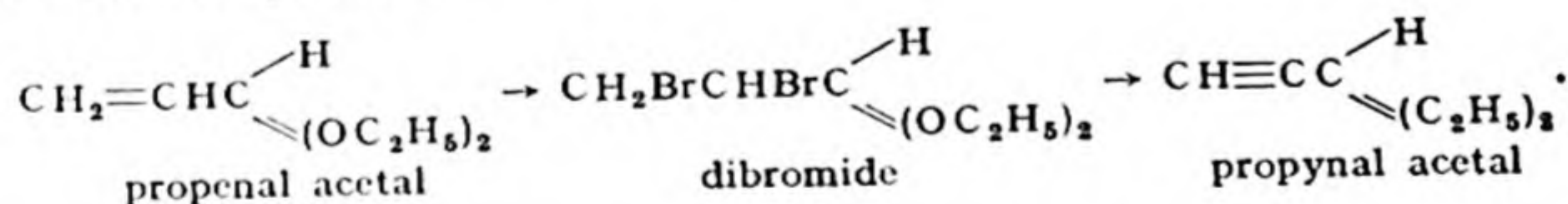
Propenal combines with two molecules of sodium bisulphite; in all probability a molecule of NaHSO_3 is added to the double bond, since only one molecule of NaHSO_3 is split off when the addition product is treated with dilute acid and propenal is not regenerated.

2-Butenal (crotonaldehyde) $\text{CH}_3\text{CH}=\text{CHCHO}$, is produced from 3-hydroxybutanal



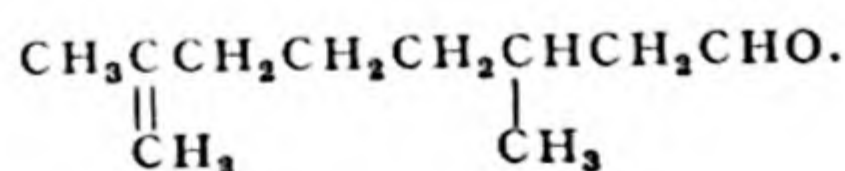
(aldol) by heating to 140° , when a molecule of water is split off. It is a liquid boiling at 105° , which is converted into crotonic acid by oxidation with silver oxide; hence its structure.

Propynal (progargyl aldehyde) $\text{CH}\equiv\text{CC} \begin{array}{l} \text{=O} \\ \text{\textbackslash H} \end{array}$, can be obtained by adding two atoms of bromine to propenal acetal and then removing two molecules of hydrogen bromide from the addition product:

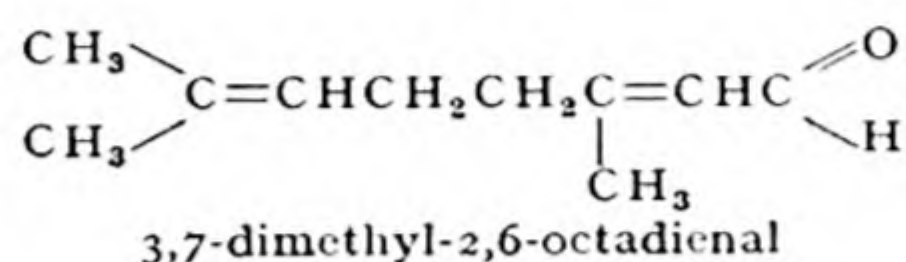


The aldehyde is obtained by warming the last mentioned acetal with dilute sulphuric acid; it is a liquid, which boils at $59-61^\circ$ and attacks the mucous membrane in the same way as acrolein.

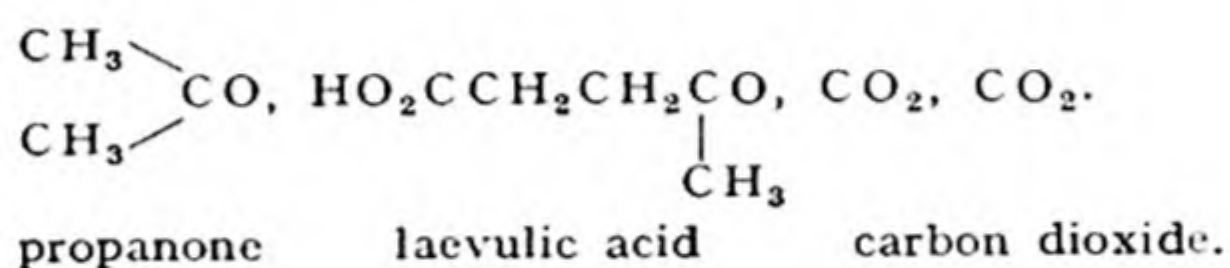
An unsaturated aldehyde of the composition $\text{C}_{10}\text{H}_{18}\text{O}$, *citronellal*, is a constituent of citronella oil, which is obtained from a tropical species of grass (*cymbopogon nardus*); citronellal has a strong odour of lemons. Its probable structure is



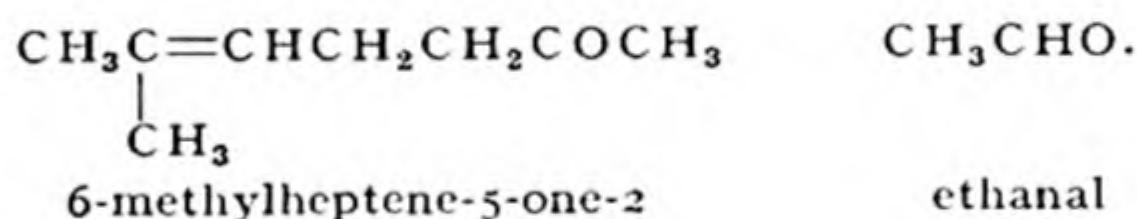
The chief component of lemongrass oil (from *cymbopogon flexosus*) is *citral*, $C_{10}H_{16}O$, b.p. 112° at 12 mm, which is also found in various other essential oils; citral has an odour of lemons and is used therefore in the perfumery industry. Geraniol (see 95) is produced by the reduction of citral; oxidation of citral with silver oxide produces *geranic acid*, $C_{10}H_{16}O_2$, (SEMMLER). This shows the presence of a $-\text{CHO}$ group in the molecule. The structure of citral is



On oxidation propanone, 3-butanone 1-carboxylic acid (laevulic acid 148) and carbon dioxide are produced.

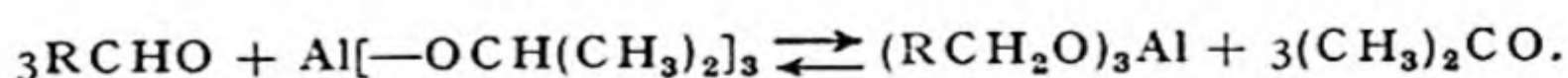


The structure of citral is confirmed by a peculiar fission which this substance undergoes on boiling with a solution of potash; a molecule of water is taken up and 6-methylhepten-5-one-2 and ethanal are formed.



The structure of this methylheptenone follows from the production of acetone and laevulic acid on oxidation. In this fission of citral the carbon chain is broken at the double bond, which is influenced by the aldehyde group.

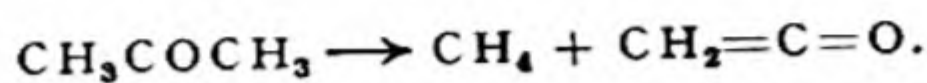
The VERLEY-MEERWEIN-PONNDORF method is particularly suited for the reduction of unsaturated aldehydes (or ketones) to unsaturated alcohols, since under these conditions only the carbonyl group and not the $\text{C}=\text{C}$ bond is reduced. On warming the aldehyde or ketone with aluminium isopropylate, a reversible reaction takes place:



The acetone is distilled off during the reaction so that the concentration of $(\text{RCH}_2\text{O})_3\text{Al}$ increases; on decomposing this compound with water the alcohol RCH_2OH is obtained.

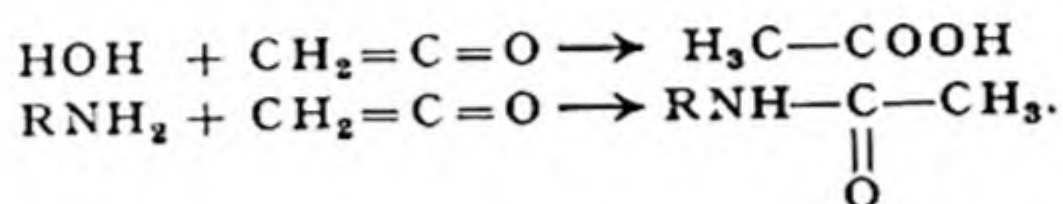
Ketenes

98. The simplest ketene, ethenone, $\text{CH}_2=\text{C}=\text{O}$, was discovered by WILSMORE and is prepared by passing acetone vapour over a glowing tungsten wire:

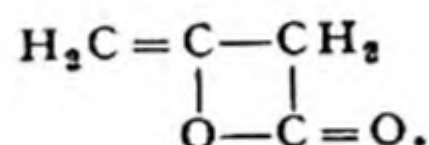


Ketene is also produced by the action of zinc on bromoacetyl bromide, $\text{BrCH}_2\text{C}(\text{Br})=\text{O}$, two bromine atoms being removed in the process; this method of formation proves the structure of the compound (STAUDINGER).

Ketene (b.p. -41° , m.p. -134°) is very poisonous; it is a very reactive substance, which gives acetic acid with water and acetyl compounds with primary amines:



Ketene easily passes into a dimer, diketene (b.p. 127°), the probable structure of which is



Ethyl acetoacetate, $\text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5$ (148, 149) is produced by the action of ethanol on diketene.

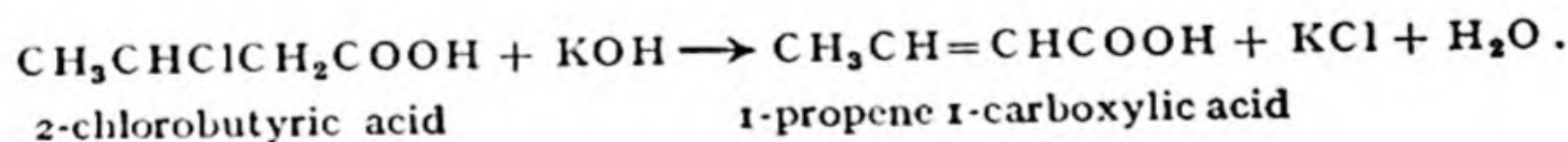
STAUDINGER has prepared a number of dialkylketenes, e.g. $(\text{CH}_3)_2\text{C}=\text{C}=\text{O}$; all these compounds are very reactive.

(xii) MONOBASIC UNSATURATED ACIDS

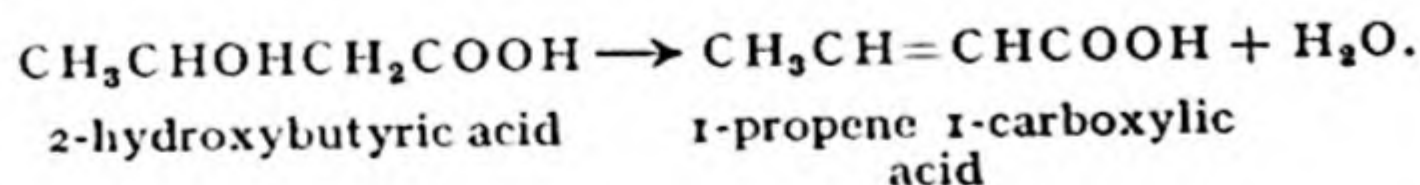
(a) *Alkene carboxylic acids* $\text{C}_n\text{H}_{2n-2}\text{O}_2$; *oleic acid series*

99. *Methods of formation.* Acids of the $\text{C}_n\text{H}_{2n-2}\text{O}_2$ series can be obtained:

1. by warming fatty acids in which a hydrogen atom in the alkyl residue is replaced by a halogen atom, (halogeno-acids, see 129), with alcoholic potash:



2. by splitting off water from mono-hydroxy-acids (see 130):



These methods of formation are analogous to the general methods of formation of alkenes from saturated compounds.

Further, unsaturated acids can be obtained by oxidising unsaturated aldehydes or by replacing the halogen atom in unsaturated halogeno-

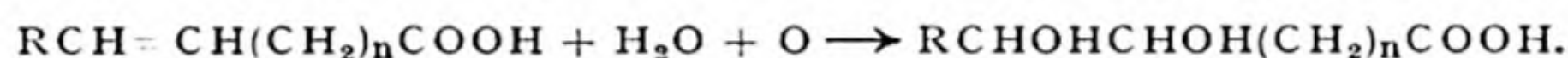
compounds of the type $\text{RCH}=\text{CHCH}_2\text{X}$ by the group $-\text{C}\equiv\text{N}$ and hydrolysing the resultant nitrile.

Nomenclature. The systematic names of these acids are derived, as with the saturated fatty acids, by putting the name "carboxylic acid" after the name of the hydrocarbon. Some also have special, trivial names derived from the substances from which the particular acid was first obtained. Thus the first member of the series, $\text{C}_3\text{H}_4\text{O}_2$, called *acrylic acid*, is followed by $\text{C}_4\text{H}_6\text{O}_2$ *crotonic acid*, $\text{C}_5\text{H}_8\text{O}_2$ *angelic acid*, $\text{C}_{18}\text{H}_{34}\text{O}_2$ *oleic acid*, $\text{C}_{22}\text{H}_{42}\text{O}_2$ *erucic acid*.

General properties. The acids of this series are "stronger" than the saturated acids with the same number of carbon atoms. The dissociation constant k (68) amounts to 0.0000134 for propionic acid, $\text{C}_3\text{H}_6\text{O}_2$, 0.000056 for acrylic acid $\text{C}_3\text{H}_4\text{O}_2$, 0.0000149 for butyric acid $\text{C}_4\text{H}_8\text{O}_2$, 0.0000204 for crotonic acid $\text{C}_4\text{H}_6\text{O}_2$, etc.

Unsaturated acids have the power of undergoing addition reactions; they can be converted into the corresponding saturated acids by reduction.

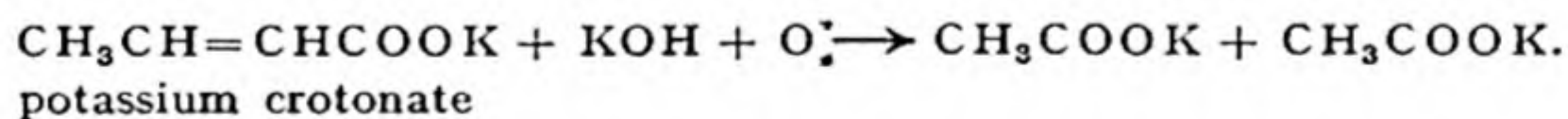
Like the alkenes, unsaturated carboxylic acids can be easily oxidised. On careful oxidation with dilute potassium permanganate solution dihydroxy-acids are first produced:



On further oxidation these acids are split up into two acids viz, RCOOH and $\text{HOOC}(\text{CH}_2)_n\text{COOH}$. Thus the position of a double bond in the molecule of an unsaturated acid can be determined in this way.

Unsaturated acids may also be broken down by the action of ozone and decomposition of the resultant ozonide (87).

Some acids of this series are split up by fusion with potassium hydroxide in presence of air, when potassium salts of saturated fatty acids are produced:

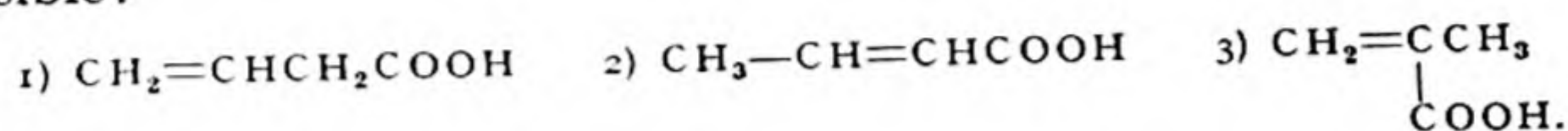


In earlier times this reaction was employed for determining structure, because it was thought that the carbon chain would be broken at the double bond. It has been shown, however, that this method is unsuitable for the purpose, because the carbon chain is broken in a place other than where the original double bond was situated. In this way acetic acid and palmitic acid are produced from oleic acid, although the latter has the structure $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$ (see 101). From this it must be concluded that the double bond in the carbon chain of an unsaturated acid can be displaced to the neighbourhood of the carboxyl group by heating with alkalis.

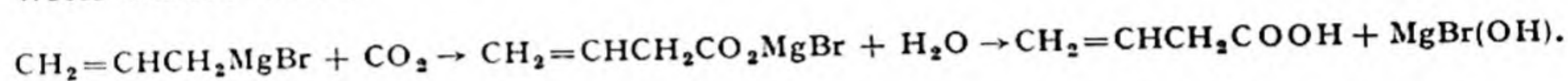
100. *Some individual members.* *Ethene carboxylic acid* or *acrylic acid*, $\text{CH}_2=\text{CHCOOH}$ is produced by the oxidation of *acrolein* $\text{CH}_2=\text{CHC} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{H} \end{smallmatrix}$

(see 97) with silver oxide or by splitting off hydriodic acid from 2-iodoethane 1-carboxylic acid, $\text{CH}_2\text{ICH}_2\text{COOH}$. Acrylic acid, b.p. 140° , m.p. 13° , has a sharp odour and is soluble in water.

Propene carboxylic acids. Replacement of a hydrogen atom in the propene molecule by a carboxyl group can occur in three different ways, so that according to the theory of structure three isomeric propene carboxylic acids are possible:

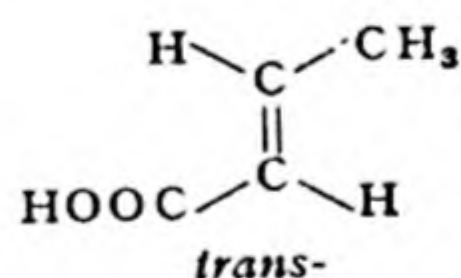
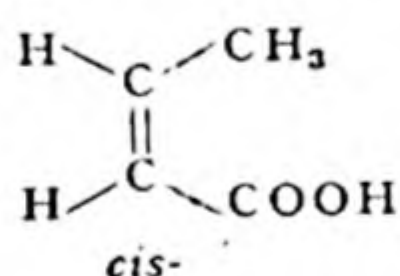


The acid of formula 1, propene-2 1-carboxylic acid or *vinylacetic acid* (b.p. 163°), can be obtained by the action of carbon dioxide on allylmagnesium bromide and decomposition of the addition product initially formed with dilute acid:

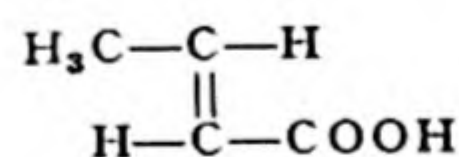
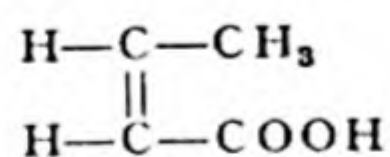


Two acids are known, both of which must be considered as being propene-1, 1-carboxylic acid (formula 2), namely, *crotonic acid* with m.p. 72° and b.p. 189° and *allocrotonic acid* (isocrotonic acid), with m.p. 15° , b.p. 169° . Both acids can be converted into butyric acid by reduction and oxalic acid and acetic acid are formed from both acids by oxidation, from which the position of the double bond is established.

Crotonic acid and allocrotonic acid are stereo-isomers, which differ in the position of the H-atoms and the CH_3 - and COOH -groups with regard to the plane of the double bond (82).



or in projection formulae:



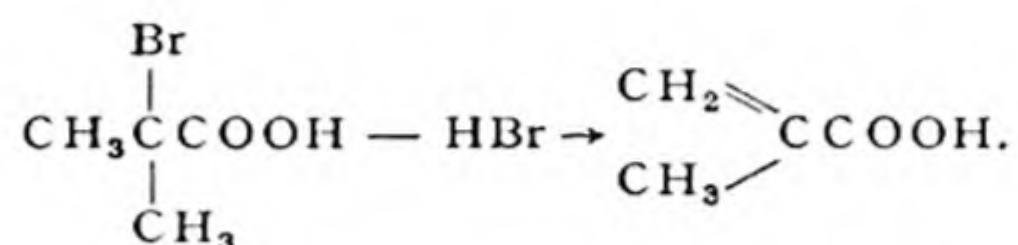
The *trans*-configuration (126) is attributed to crotonic acid. Stereoisomeric forms (*cis-trans* forms) of a number of homologues of crotonic acid are also known.

Crotonic acid occurs in croton oil. Allocrotonic acid is partially converted into crotonic acid on heating.

Crotonic acid can be obtained by the action of potassium cyanide on allyl iodide, $\text{CH}_2=\text{CHCH}_2\text{I}$, followed by hydrolysis of the resultant allyl cyanide, $\text{CH}_2=\text{CHCH}_2\text{CN}$. Thus during the conversion of allyl cyanide into crotonic acid, the double bond must

be displaced, because allyl cyanide still has the structure ascribed to allyl iodide as is shown by an examination of the molecular refraction. The molecular refraction for the α -line in the hydrogen spectrum is 19.75 for allyl cyanide C_3H_5CN and 20.28 for propane carbonitrile, C_3H_7CN . The difference $[H_2]$ is therefore 0.53, which agrees with a terminal double bond (see 84).

An acid of formula 3, *1-methylethene 1-carboxylic acid* or *methacrylic acid*, is produced by splitting off hydrogen bromide from 1-bromo-1-methylethane 1-carboxylic acid:



Methacrylic acid, b.p. 161° , m.p. 15° , occurs in *Roman camomile* oil.

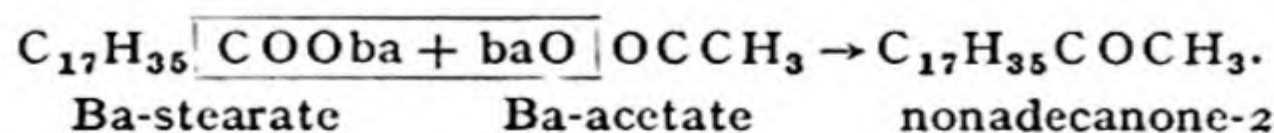
Angelic acid $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$ occurs as the ester in the roots of *angelica archangelica*; it melts at 45° ; *tiglic acid*, m.p. 64° , which also occurs, for example, in *Roman camomile* oil, is a stereo-isomer of angelic acid.

101. *Oleic acid* or *heptadecene-8 1-carboxylic acid*, $C_{18}H_{34}O_2$, is the most important member of the series of alkene carboxylic acids. Glycerides of oleic acid, *i.e.* glycerol esters, in which an oleic acid residue occurs, are constituents of most vegetable and animal fats (114). The oleic acid can be separated from these substances by hydrolysis; a large proportion of oleic acid together with a little stearic acid and palmitic acid is obtained from the liquid fats, *e.g.* olive oil, by saponification. The lead salt of oleic acid is soluble in ether and alcohol and can therefore be separated from the lead salts of saturated fatty acids which are much less soluble in these solvents.

Oleic acid is dimorphous, the stable modification melts at 16.1° , the metastable at 13.2° ; it is odourless, the liquid is viscous, very slightly soluble in water but miscible in all proportions with alcohol and ether. Oleic acid boils at 223° at 10 mm; it cannot be distilled at ordinary pressure without decomposition.

On catalytic reduction, oleic acid takes up two atoms of hydrogen with the production of stearic acid. Thus oleic acid has a normal carbon chain.

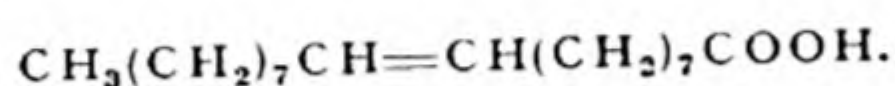
The normal structure of stearic acid has been proved by KRAFFT by converting it into a succession of acids with a smaller number of carbon atoms in the following way. A mixture of barium stearate and barium acetate was heated in a vacuum, when a ketone, $C_{17}H_{35}\text{COCH}_3$, was produced.



When this ketone was oxidised, acetic acid and an acid $C_{17}H_{34}O_2$, were produced. From this it follows that the ketone must have a CH_2 -group next to the carbonyl

group *i.e.* it must be $C_{16}H_{33}CH_2COCH_3$, since only in this case can an acid with 17 carbon atoms be produced in the oxidation. This acid, $C_{17}H_{34}O_2$, was converted in the same way into a ketone $C_{16}H_{33}COCH_3$, which was oxidised to produce an acid $C_{16}H_{32}O_2$. Therefore $C_{17}H_{34}O_2$ must be $C_{15}H_{31}CH_2COOH$ and $C_{18}H_{36}O_2$ must be $C_{15}H_{31}CH_2CH_2COOH$. The acid $C_{16}H_{32}O_2$ (palmitic acid) was converted into a ketone, and so on. This procedure was repeated until an acid $C_{10}H_{20}O_2$, *nonane 1-carboxylic acid* was obtained, which was known by synthesis (148) to possess a normal carbon chain.

The position of the double bond in the molecule of oleic acid follows from the oxidation of methyl oleate with potassium permanganate when two acids each containing 9 carbon atoms, namely, octane 1-carboxylic acid or *pelargonic acid*, $CH_3(CH_2)_7COOH$ and heptane 1,7-dicarboxylic acid or *azelaic acid*, $HOOC(CH_2)_7COOH$ (see 124). The structure of oleic acid is therefore

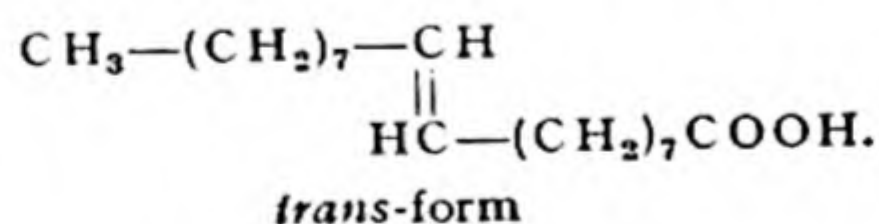
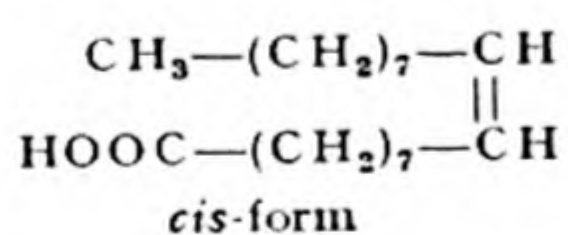


This structural formula is confirmed by the action of ozone on oleic acid; an ozonide (see 87) is produced, from which *pelargonic aldehyde* $CH_3(CH_2)_7CHO$ and an aldehydic acid, $OHC(CH_2)_7COOH$, are obtained by warming with water. These aldehydes can be converted into *pelargonic acid* and *azelaic acid* by further oxidation. Oleic acid is slowly oxidised by air, especially under the influence of light.

The conversion of oleic acid into a stereo-isomeric compound, *allo-oleic acid* or *elaidic acid*, which melts at 47° , is noteworthy. This transformation (*elaidinisation*) takes place when a solution of oleic acid in acetone is treated with nitrous gases at 0° or when oleic acid is heated to 220° with a little selenium with the exclusion of oxygen.

Elaidic acid can be converted into stearic acid by reduction. The double bond in elaidic acid lies between the ninth and tenth carbon atoms, since on degradation with ozone the same degradation products are obtained as from oleic acid.

These stereo-isomeric acids are represented therefore by the following formulae :



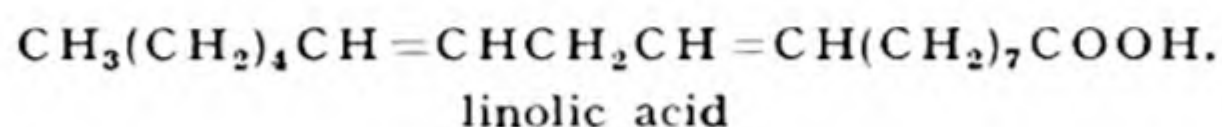
It is not yet known with certainty whether oleic has a *cis*- or a *trans*-configuration.

Erucic acid $C_{22}H_{42}O_2$, m.p. 34° . A glyceryl ester of this acid occurs in rape oil, the oil from rape seed (*brassica campestris*) and in mustard oil. The structure $CH_3(CH_2)_7CH=CH(CH_2)_{11}COOH$, is derived from the products obtained on oxidation. Erucic acid is converted into a stereoisomeric compound, *allo-erucic acid* or *brassidic acid* melting at 65° , by the action of nitrous acid.

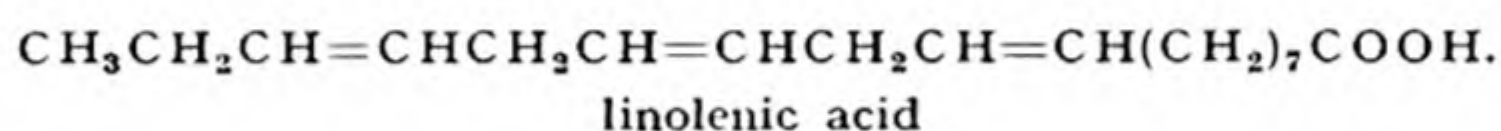
(b) *Unsaturated acids with two and three double bonds*

102. Glycerides (**114**) of *linolic acid* $C_{18}H_{32}O_2$, occur in many vegetable oils, e.g. in *poppy-seed oil*, *ground-nut oil* and *linseed oil*; linseed oil also contains glycerides of *linolenic acid*, $C_{18}H_{30}O_2$. Both acids can be converted into stearic acid by catalytic hydrogenation.

From the oxidation of linolic acid (in the form of its methyl ester) with potassium permanganate, heptane 1,7-dicarboxylic acid, pentane 1-carboxylic acid and malonic acid are obtained, from which it follows that the structure is:



In the degradation of the ethyl ester of linolenic acid with ozone, the mono-ester of heptane 1,7-dicarboxylic acid, propionaldehyde and malonic acid are obtained; the structure of linolenic acid is therefore:



Linolic acid and linolenic acid and the esters of these acids are easily oxidised by atmospheric oxygen, when polymerisation also occurs (drying oils see **114**). Four stereo-isomers are possible for a compound with the structure of linolic acid. Since *cis-trans*-isomerism can occur at each of the double bonds (I and II), there are four combinations, *cis*_I-*cis*_{II}; *trans*_I-*trans*_{II}; *cis*_I-*trans*_{II}; *trans*_I-*cis*_{II}. So far only one linolic acid has been found amongst the fission products of vegetable oils.

The polymerisation of alkenes and vinyl compounds

103. Under certain conditions alkenes can polymerise; this tendency to polymerisation is much more pronounced in compounds of the type $CH_2=CHX$ in which X represents a halogen atom, a $-COOH$ or $-COOR$ group, a $-CHO$ group, etc.

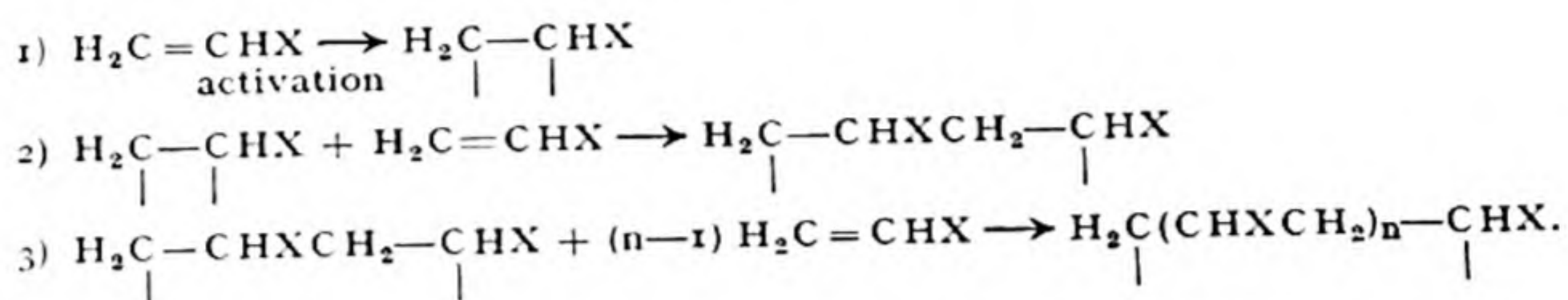
As a result of this polymerisation polymers with a very high molecular weight can be obtained, which find a wide application in the manufacture of various articles for every-day use or as construction materials (artificial resins, plastics, artificial rubber etc.).

All polymerisations of alkenes and their derivatives take place exothermally. The alkenes themselves—and also some of their derivatives of the type $CH_2=CHX$ —do not polymerise at ordinary temperatures and pressures because the energy of activation of the reaction is too high. On the basis of the work of various investigators (MARK, RIDEAL, STAUDINGER, EVANS) the following scheme has been developed:

A molecule of the monomer is activated by the absorption of a light

quantum or by thermal collisions, *i.e.* it is brought into a state with a higher energy content (1). The activated molecule can then react with a non-activated monomer-molecule, as a result of which heat is evolved due to the reaction and a dimer-molecule is produced (2), which is also in an activated state (*i.e.* in a state of higher energy compared with the ground state).

For simplification "free valencies" are assumed to be present in activated molecules in the equations given below:



The polymerisation therefore takes place by a chain-reaction. The activation of the monomer (1) can be promoted by light of short wave-length or by catalysts such as peroxides, oxygen, aluminium chloride, boron fluoride etc. Reaction 3 determines the growth of the carbon chain of the polymer. This reaction proceeds until the chain-reaction is broken by the activated polymer molecule losing its excess energy, for example, by collisions against the wall of the vessel or by interaction with other molecules.

Small quantities of phenol, and especially of hydroquinone (quinol), have the power of breaking the chain-reaction, so that these substances are added when it is desired to prevent polymerisation of the monomer (61).

A third possibility of breaking the chain reaction exists when the activated polymer molecule assumes a cyclic structure.

The degree of polymerisation, *i.e.* the number of molecules of monomer, from which a polymer is built, is determined by the number of successive chain reactions. Absence of impurities, which may break the reaction chain, promotes a high degree of polymerisation. Formation of a large number of activated monomer-molecules, each of which can act as a "polymerisation nucleus" (STOBBE), leads to the formation of polymers with a low degree of polymerisation. Thus the final product of the polymerisation does not consist of a single kind of molecule, but of molecules having various degrees of polymerisation, *i.e.* different molecular weights; it is a mixture of *polymer-homologues*. In some cases, different fractions having different average degrees of polymerisation, can be separated by fractional precipitation from a solution of the original polymerisate.

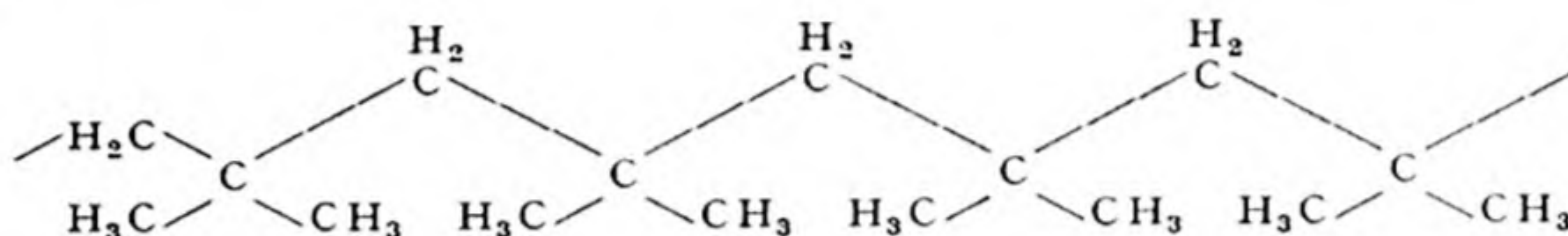
According to equations 2 and 3 in the above reaction scheme, in the polymerisation of $\text{CH}_2=\text{CHX}$, long-chain molecules are formed in which side-chains (the groups X) may be substituted. In such a case the products are referred to as *linear polymers*. It must be assumed that the unsaturated

terminal groups combine by forming large rings—with the production of very large cyclic chains—or, that saturated terminal groups are produced by interaction with small quantities of foreign substances. The polymerisates produced from linear polymers, are *thermoplastic*, *i.e.* they cannot be converted into hard, non-plastic products by heating.

A few examples of this group of polymers are given below.

When ethene is submitted to pressures of 1200 atm. at a temperature of 200°, polymers $(CH_2)_x$ with a molecular weight between 3,000 and 40,000 (*polythene*) are produced.

Depending on the actual conditions employed, liquid or solid polymers having a carbon chain substituted by methyl groups, are obtained from isobutene by polymerisation at low temperatures with boron fluoride as catalyst.



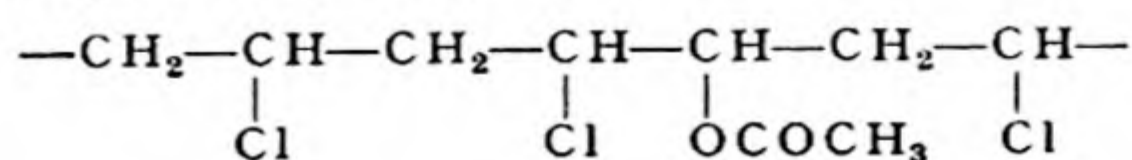
The polymers of styrene or phenylethene, $C_6H_5CH=CH_2$, (267) colourless transparent products of amorphous structure, are of great practical importance.

These polymers of ethene, isobutene and styrene possess high insulating power for electricity and good dielectric properties; at the same time these polymeric hydrocarbons are stable towards various chemical reagents. On this account they find application in the electrotechnical industries and for many other purposes.

Other important starting materials for the preparation of synthetic resins and plastic materials are vinyl chloride, (94) vinyl acetate (95) and the esters of acrylic and methacrylic acids (100). The polymerisation of these liquid starting materials is carried out both on the pure material and also on aqueous emulsions, which are produced with the aid of emulsifying agents, *e.g.* salts of sulphonated oils. Peroxides, *e.g.* benzoyl peroxide (260) or hydrogen peroxide, are used as catalysts for the polymerisation.

Transparent, water-clear materials, which are used as “unbreakable glass” for many purposes, *e.g.* in aeroplanes and motor cars, are obtained by polymerising esters of acrylic acid or methacrylic acid.

Copolymerisation is of considerable technical importance. In this process a mixture of two different starting materials is subjected to polymerisation, *e.g.* a mixture of vinyl chloride and vinyl acetate. In this way a polymer containing both components is produced:

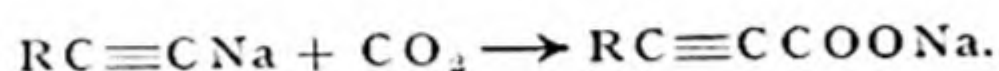


By using copolymerisation it is possible to introduce different variations into the preparation of polymerisates, and the properties of the final product can be modified.

(c) *Monobasic unsaturated acids with a triple bond, $C_nH_{2n-4}O_2$; the propiolic acid series*

104. The first member of this series is *propiolic acid, ethyne carboxylic acid*, $HC\equiv CCOOH$, m.p. 9° and b.p. 92° at 50 mm.

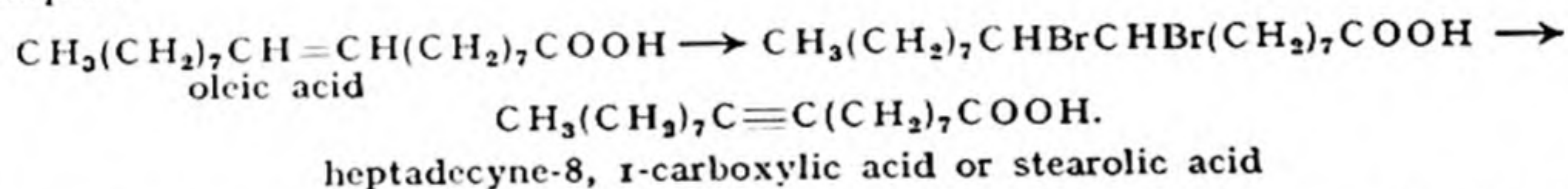
The sodium salts of the acids of this series can be obtained by the action of carbon dioxide on the sodium derivatives of alkynes:



By this synthesis, acids are obtained in which the carboxyl group is directly attached to the triply bound carbon atom. The silver salts of these acids readily decompose into carbon dioxide and alkynesilver, $RC\equiv CAg$.

Acids with a triple bond can, in general, be prepared by adding bromine to an alkene carboxylic acid and splitting off two molecules of hydrogen bromide from the dibromoalkane carboxylic acid so obtained.

Example:



Under the influence of sulphuric acid this acid combines with a molecule of water, in the same way as alkynes can add on water. In this case 9-ketoheptadecane 1-carboxylic acid (*ketostearic acid*), $CH_3(CH_2)_7COCH_2(CH_2)_7COOH$, is produced.

The oxime of this ketonic acid $CH_3(CH_2)_7C(CH_2)_8COOH$, can be converted into a



substituted acid amide, $CH_3(CH_2)_7CONH(CH_2)_8COOH$, (BECKMANN transformation, see 59) by the action of concentrated sulphuric acid.

The structure of this compound follows from the result of fission with fuming hydrochloric acid whereby octane 1-carboxylic acid, $CH_3(CH_2)_7COOH$, and 8-amino-octane 1-carboxylic acid, $H_2N(CH_2)_8COOH$, are produced. This was the first proof of the position of the double bond in oleic acid (BARUCH 1894).

CHAPTER 8

COMPOUNDS WITH TWO OR MORE CHARACTERISTIC ATOMS OR GROUPS OF ATOMS

105. So far, the only compounds which have been discussed are those which can be derived from alkanes or alkenes by replacing *one* hydrogen atom therein by a monovalent atom or a monovalent group of atoms, such as halogen, hydroxyl, carboxyl, etc. (27). Compounds will now be discussed, in which *two or more* of these characteristic atoms or atomic groupings occur. Polyvalent compounds are also met with, for, in a substance CH_2X_2 , CH_2 may be considered as a bivalent radical.

(i) HALOGENO-DERIVATIVES OF ALKANES

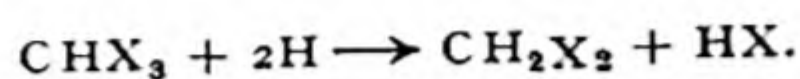
106. A mixture of CH_3Cl , CH_2Cl_2 , CHCl_3 and CCl_4 (17) is produced by the action of chlorine on methane. The ratio in which these various compounds are formed depends on the proportion of the reagents. The reaction takes place at ordinary temperature in the light and at about 400° in the dark. A similar mixture of substitution products is produced by the action of bromine on methane. The action of fluorine on methane is very violent and tetrafluoromethane is formed, on the other hand, iodine does *not* react with alkanes.

By the action of chlorine or bromine on homologues of methane, in general there are produced along with mono-substitution products (of which different isomers may be formed from propane and the higher homologues) also compounds of the types $\text{C}_n\text{H}_{2n}\text{X}_2$, $\text{C}_n\text{H}_{2n-1}\text{X}_3$, etc. Isomers are possible with compounds containing more than one halogen atom because the latter may occupy various positions in the molecule. The halogeno-derivatives of the hydrocarbons are usually prepared by other means because direct chlorination or bromination of alkanes leads to a complex mixture of compounds.

The monohalogeno-alkanes or alkyl halides have already been discussed (39). Some compounds with more than one halogen atom in the molecule will now be dealt with.

Halogeno-derivatives of methane. Compounds of the type CH_2X_2 are

prepared by partial reduction of the trihalogeno-compounds CHX_3 . Thus *dichloromethane*, *methene chloride* or *methylene dichloride*, is prepared by the action of zinc and hydrochloric acid on an alcoholic solution of trichloromethane:

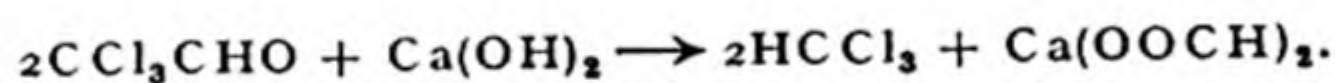


Diiodomethane, *methene iodide* can be prepared by the reduction of triiodomethane with hydriodic acid and phosphorus. Some physical constants are given in Table 30.

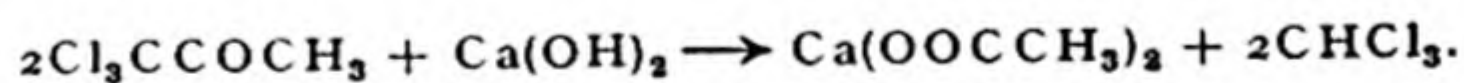
TABLE 30
SOME PHYSICAL CONSTANTS OF DIHALOGENOMETHANES

Name	Formula	M.p.	B.p.	Density d_4^{15}
Dichloromethane	CH_2Cl_2	-96.5°	40.2°	1.3348
Dibromomethane	CH_2Br_2	-52.7°	97.0°	2.5099
Diiodomethane	CH_2I_2	6.1°	68° at 12 mm	3.3345

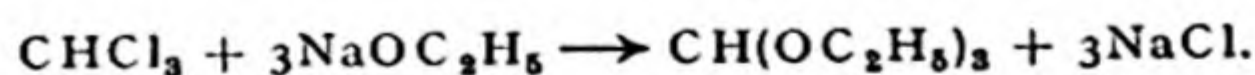
Trichloromethane, *chloroform* CHCl_3 . This compound is obtained by warming ethanol with bleaching powder (chloride of lime). In this process the bleaching powder acts both as a chlorinating and as an oxidising agent, as a result of which trichloroacetaldehyde CCl_3CHO is first produced (see 128), a substance, which is split up into formic acid (as calcium salt) and chloroform by bases (in this case by the lime present in the bleaching powder):



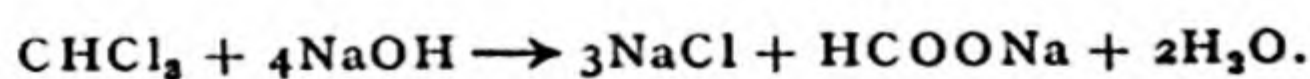
Chloroform was discovered in this way in 1831 by LIEBIG and by SOUBEIRAN. It is also prepared from acetone and bleaching powder; in this case *trichloroacetone* is produced as an intermediate and is decomposed by lime into chloroform and calcium acetate:



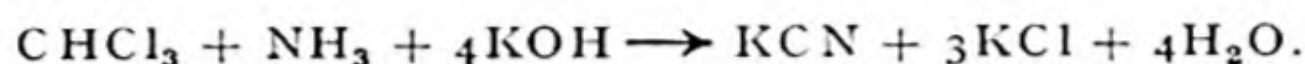
Chloroform boils at 61.2° , freezes at -63.5° , has a sweet smell and a specific gravity of 1.4891 at 20° . It is a colourless liquid, which is very slightly soluble in water. By the action of sodium ethylate on chloroform, *triethoxymethane* or *ethyl orthoformate* is formed:



Chloroform is also decomposed by warming with alkalis with the formation of an alkali formate:



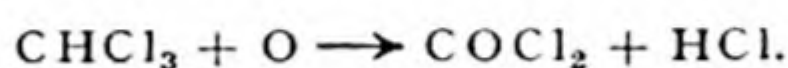
DUMAS, who discovered this reaction, considered trichloromethane as a derivative of formic acid and called it therefore chloroform. When chloroform is warmed with alcoholic ammonia and potassium hydroxide, potassium cyanide is formed:



The analogous formation of carbylamines from chloroform, alcoholic alkali and primary amines has already been mentioned in 56.

In 1847 SIMPSON found that the inhalation of chloroform vapour produced unconsciousness, after which chloroform came into use as an anaesthetic in surgical operations.

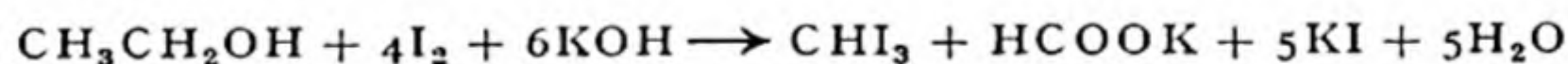
Chloroform is oxidised by air under the influence of sunlight with the production of hydrogen chloride and *carbon oxychloride* or *phosgene* (COCl_2):



Phosgene is a very powerful respiratory poison. Hence 1 % of ethanol is added to chloroform for medicinal uses to retard the decomposition mentioned above, while at the same time, carbon oxychloride is converted by ethanol into diethyl carbonate, which is non-poisonous.

107. *Tribromomethane, bromoform* (b.p. 149.2° , freezing point 8.3° , spec. grav. 2.9035 at 15°) is produced by the action of potassium hypobromite on acetone. Bromoform is used in medicine.

Triiodomethane, iodoform CHI_3 . This substance can be prepared by treating ethanol with potash (or potassium hydroxide) and iodine. The intermediate product, CI_3CHO , which would be expected on analogy with the preparation of chloroform, cannot be isolated. The equation



represents the total course of the reaction.

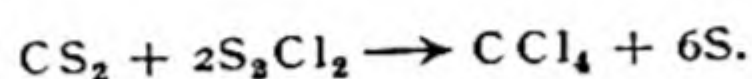
In the technical preparation of iodoform a solution of soda and potassium iodide in dilute alcohol or acetone is subjected to electrolysis; iodine is produced at the anode and reacts with the alcohol or acetone in the alkaline liquid with the formation of iodoform.

Iodoform crystallises in yellow hexagonal platelets, which show dichroism (yellow and green); it is volatile, has a characteristic saffron-like odour and melts at 119° ; it is very slightly soluble in water. On account of these characteristic properties the formation of iodoform is a test for ethanol (see 32), but it must be remembered, however, that acetaldehyde, acetone and propanol-2 also give the same reaction. In general, compounds in which a methyl group is attached to a $-\text{CH}_2\text{OH}$, $>\text{CHOH}$, $-\text{CHO}$ or $>\text{C}=\text{O}$ group, react with alkaline iodine solution with the formation of iodoform.

The iodoform reaction is much more sensitive for acetone and acetaldehyde than for ethanol.

Iodoform is used as an antiseptic in the treatment of wounds. Itself, it has practically no bactericidal action, but iodine is liberated from it by the secretions in the wound and this accounts for its antiseptic action.

Tetrachloromethane or *carbon tetrachloride* CCl_4 , can be obtained by the total chlorination of methane. This substance is prepared commercially by heating together carbon disulphide and sulphur chloride in presence of iron chloride as a catalyst:



Carbon tetrachloride is produced in very small quantities by the action of chlorine on pure, "amorphous" carbon at $400-500^\circ$; thus this represents a synthesis from the elements. Tetrachloromethane is a colourless liquid, boiling at 76.7° , melting at -22.9° and having a specific gravity of 1.5940 at 20° . Carbon tetrachloride is an excellent solvent for oils, fats, waxes and resins; it is used commercially for this purpose and has the advantage over petrol in being noninflammable.

Tetrabromomethane, CBr_4 , can be obtained from carbon disulphide and bromine; it melts at 91.0° and boils at 102° at a pressure of 50 mm.

Tetraiodomethane, CI_4 , is unstable; it decomposes on warming with the separation of iodine.

By the action of antimony trifluoride (SbF_3) on carbon tetrachloride one or more of the chlorine atoms can be replaced by fluorine atoms (SWARTS), by which method carbon tetrahalides such as CCl_3F , CCl_2F_2 or CClF_3 are produced. The halogen atoms in these compounds are very unreactive; CCl_2F_2 (b.p. -29.8°) is used in refrigerators (MIDGLEY).

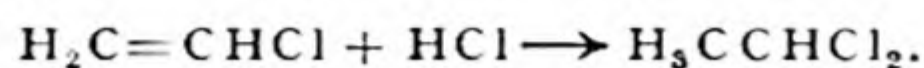
108. Halogeno-derivatives of the homologues of methane. Halogenoalkanes in which two halogen atoms are combined on adjacent carbon atoms, are most readily available. These compounds are prepared by addition of halogen to alkenes.

1,2-Dichloroethane, $\text{ClCH}_2\text{CH}_2\text{Cl}$, is obtained by the action of chlorine on ethene; it is a colourless liquid, b.p. 83.5° , spec. grav. 1.2600 at 15° .

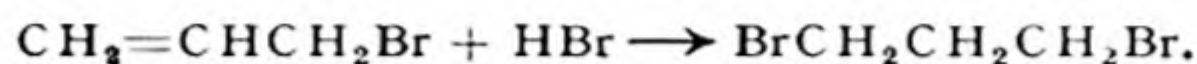
Dichloro- or dibromo-alkanes in which the two halogen atoms are attached to the same carbon atom, can be prepared by the action of PCl_5 or PBr_5 on aldehydes or ketones.

1,1-Dichloroethane can also be obtained by addition of two molecules of hydrogen chloride to ethyne. This reaction takes place in two stages; when a mixture of ethyne and gaseous hydrogen chloride is passed over finely divided mercuric chloride as a catalyst at ordinary temperatures, practically all the ethyne is converted into vinyl chloride, $\text{H}_2\text{C}=\text{CHCl}$, even if an excess of hydrogen chloride is present. The reaction

represented below takes place at 100° in presence of a zinc chloride catalyst (WIBAUT and VAN DALFSEN):



1,3-Dibromopropane, a substance which has been used in various syntheses, is prepared by the action of anhydrous hydrogen bromide on allyl bromide in sunlight:



When this reaction is carried out in the dark, along with *1,3-dibromopropane* there is also produced *1,2-dibromopropane*, which is identical with the product obtained by the addition of bromine to propene; the structures of both dibromopropanes can be deduced from these reactions.

Tetrahalogenoalkanes in which two halogen atoms are attached to each of two adjacent carbon atoms, are obtained by the addition of halogen to alkynes.

1,1,2,2-Tetrachloroethane, b.p. 146.2° , is prepared commercially by passing chlorine and acetylene into antimony pentachloride, which acts catalytically. The tetrachloroethane so obtained serves as a solvent in this reaction. *Trichloroethene*, $\text{CCl}_2=\text{CHCl}$, b.p. 88° , is obtained by heating tetrachloroethane with lime and water. Trichloroethene is poisonous.

1,2-Dichloroethene (b.p. of the *cis*-form 47.7° ; of the *trans*-form 60.5° , compare 126) is prepared by treating tetrachloroethane with zinc dust and water. All these compounds are good, noninflammable solvents for sulphur, oils and fats. They are used for the extraction of oils and in the vulcanisation of rubber.

Hexachloroethane, C_2Cl_6 , sublimes at 186° and melts at 187° . This substance is produced amongst others by the interaction of carbon and chlorine by maintaining an electric arc between carbon electrodes in a vessel filled with chlorine.

According to recent investigations, aliphatic hydrocarbons can be completely fluorinated by heating with cobalt trifluoride, which is converted into cobalt difluoride in the process; the latter substance is again converted into cobalt trifluoride by the action of gaseous fluorine. In this way, a large number of *fluoro-hydrocarbons* of the type $\text{C}_n\text{F}_{2n+2}$ containing 2 to 16 carbon atoms have been prepared. It is remarkable that these compounds are very stable and very unreactive in a chemical sense. The boiling points of these compounds do not differ appreciably from those of the corresponding hydrocarbons.

(ii) COMPOUNDS WITH TWO OR MORE ALCOHOL GROUPS (POLYHYDRIC ALCOHOLS)

109. Compounds of the type $\text{C}_n\text{H}_{2n}(\text{OH})_2$, can be obtained by replacing both halogen atoms in dihalogenoalkanes by hydroxyl groups. Experience has shown that this reaction leads to the desired compounds only when the halogen atoms are attached to different carbon atoms, as for example, in $\text{CH}_2\text{XCH}_2\text{X}$ or $\text{CH}_2\text{XCH}_2\text{CH}_2\text{X}$. If however, a dihalogeno-compound of the type RCHX_2 is submitted to a reaction by which the halogen atoms would be replaced by hydroxyl, instead of the compound $\text{RCH}(\text{OH})_2$ there is produced a substance containing one molecule of water less, namely, an

alkanal RCHO . Thus by the action of silver acetate on RCHX_2 a compound $\text{RCH}(\text{OOCCH}_3)_2$ is obtained, which may be regarded as the acetate of the hypothetical compound $\text{RCH}(\text{OH})_2$. When an attempt is made to split this acetate hydrolytically, the aldehyde RCHO and not the compound $\text{RCH}(\text{OH})_2$ is obtained.

Ethers of the type $\text{RCH}(\text{OC}_2\text{H}_5)_2$ on the other hand are stable; they are the *acetals* (see 60). When a trihalogeno-compound of the type RCX_3 is treated with sodium alcoholate, a compound $\text{R}-\text{C}(\text{OC}_2\text{H}_5)_3$, an *ortho-ester*, (106) is produced. This compound on hydrolysis does not give the compound $\text{RC}(\text{OH})_3$ but the corresponding carboxylic acid RCOOH , with the removal of water.

In general, compounds in which more than one hydroxyl group is attached to the same carbon atom, are not stable.

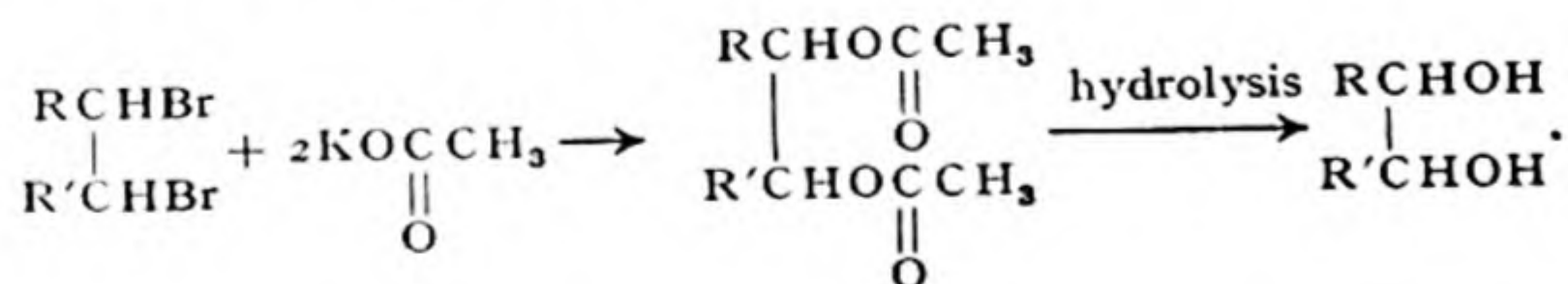
Later on we shall learn of some kinds of compounds with two hydroxyl groups attached to one carbon atom, which are stable (see 128).

On the other hand, many polyhydric alcohols are known in which the hydroxyl groups are attached to different carbon atoms. The more important will be discussed below.

(a) *Alkanediols, glycols (dihydric alcohols)*

110. These compounds are produced in precisely the same way as the monohydric alcohols, from the corresponding halogeno-compounds. A. WURTZ tried in 1859 to prepare dihydric alcohols similar to the already known trihydric alcohol glycerol. He succeeded by boiling dibromoalkanes (obtained by addition of bromine to alkenes) with silver acetate and hydrolysing the resultant esters.

This method of preparation is still used, but potassium acetate is usually employed instead of silver acetate:

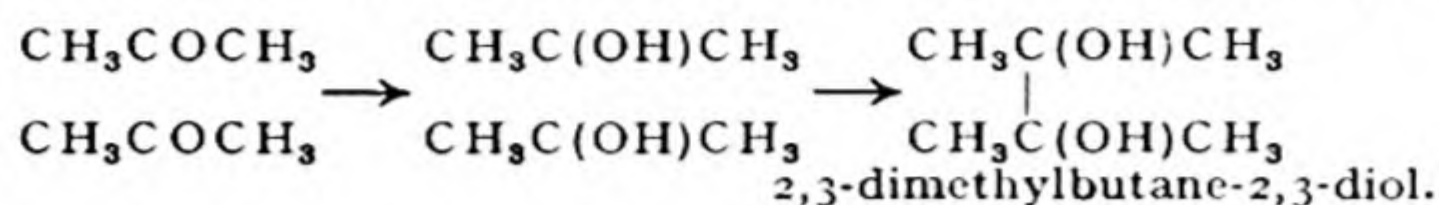


The replacement of the halogen atoms in the halogeno-compounds by hydroxyl groups may occur in some cases by boiling with a solution of soda or with lead oxide and water.

Glycols of the type RCHOHCHOHR , may be prepared also by careful oxidation of alkenes in aqueous solution.

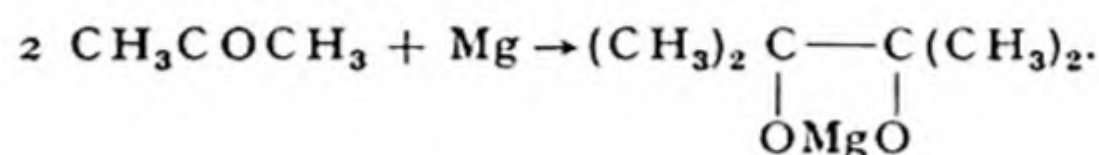
Alkanediols with branched carbon chains and two hydroxyl groups on adjacent carbon atoms may be prepared along with secondary monohydric alcohols by reducing

ketones. This may be so represented that each molecule of ketone takes up only one atom of hydrogen and the unsaturated residues (free radicals) so obtained then combine :



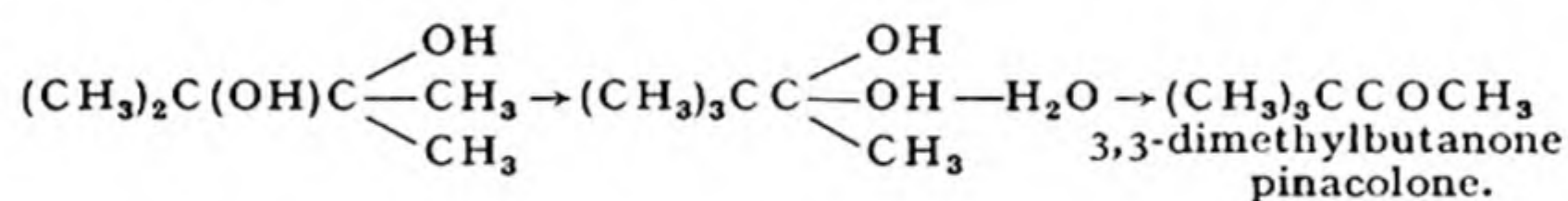
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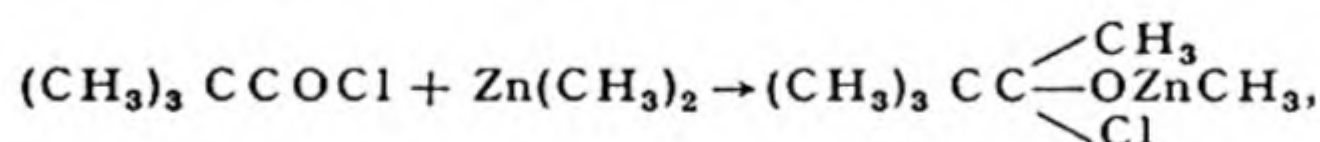


This compound is decomposed by water into magnesium oxide and $(\text{CH}_3)_2\text{COHCOH}(\text{CH}_3)_2$. The 2,3-dimethylbutane-2,3-diol so obtained, crystallises with 6 molecules of water of crystallisation in large, plate-like crystals; hence this dihydric alcohol is called *pinacol* ($\pi\nu\alpha\zeta$ = table).

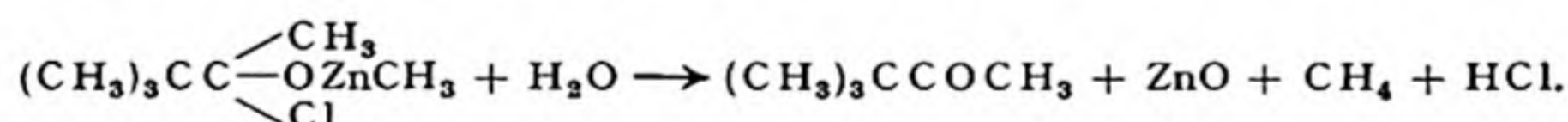
Pinacol undergoes a remarkable transformation on distillation with dilute sulphuric acid, water being split off and a ketone produced. It may be imagined that a hydroxyl group and a methyl group change places before a molecule of water is split off thus :



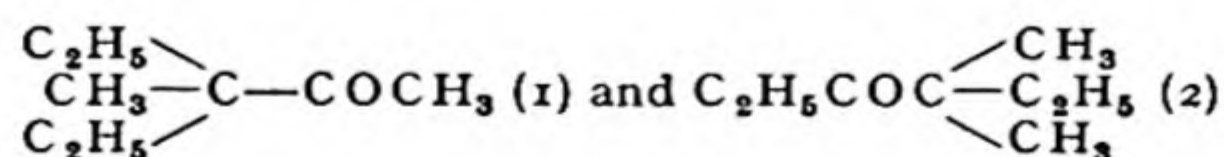
The 3,3-dimethylbutanone formed in this way, was previously called *pinacoline*; the name *pinacolone* is to be preferred however. This reaction is referred to as the *pinacoline* or better as the *pinacolone transformation*. The structure of pinacolone follows, for example, from its synthesis from the chloride of trimethylacetic acid (1,1-dimethylethane-1-carbonyl chloride), $(\text{CH}_3)_3\text{CCOCl}$, and dimethylzinc :



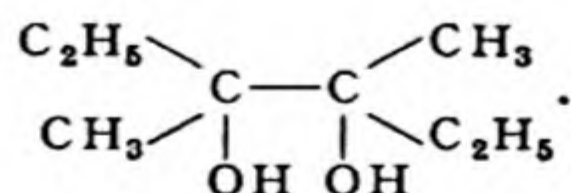
the addition product being decomposed with water :



Homologues of pinacol also may undergo a pinacolone transformation (MONTAGNE; TIFFENEAU). Thus two isomeric ketones :



may be produced from



alkanal RCHO . Thus by the action of silver acetate on RCHX_2 a compound $\text{RCH}(\text{OOCCH}_3)_2$ is obtained, which may be regarded as the acetate of the hypothetical compound $\text{RCH}(\text{OH})_2$. When an attempt is made to split this acetate hydrolytically, the aldehyde RCHO and not the compound $\text{RCH}(\text{OH})_2$ is obtained.

Ethers of the type $\text{RCH}(\text{OC}_2\text{H}_5)_2$ on the other hand are stable; they are the *acetals* (see 60). When a trihalogeno-compound of the type RCX_3 is treated with sodium alcoholate, a compound $\text{R}-\text{C}(\text{OC}_2\text{H}_5)_3$, an *ortho-ester*, (106) is produced. This compound on hydrolysis does not give the compound $\text{RC}(\text{OH})_3$ but the corresponding carboxylic acid RCOOH , with the removal of water.

In general, compounds in which more than one hydroxyl group is attached to the same carbon atom, are not stable.

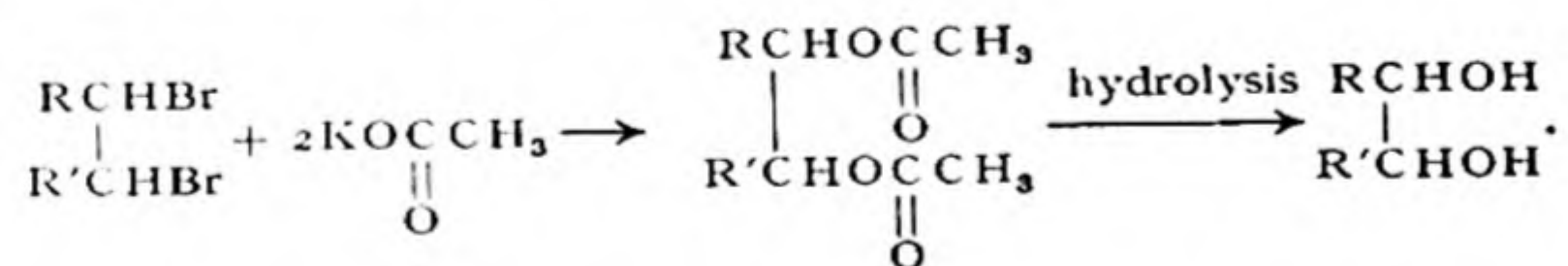
Later on we shall learn of some kinds of compounds with two hydroxyl groups attached to one carbon atom, which are stable (see 128).

On the other hand, many polyhydric alcohols are known in which the hydroxyl groups are attached to different carbon atoms. The more important will be discussed below.

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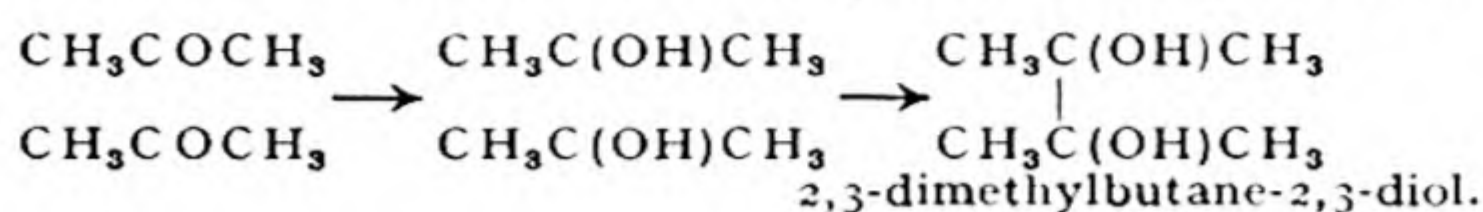


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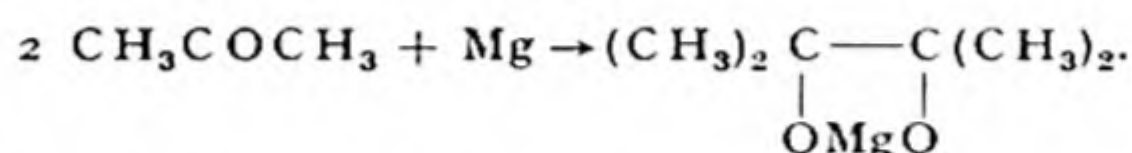
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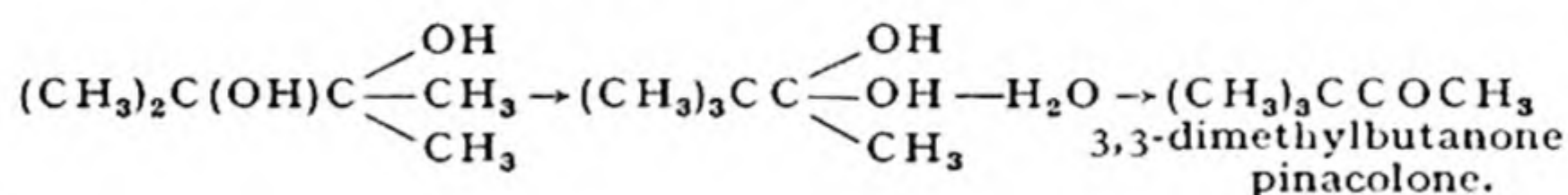
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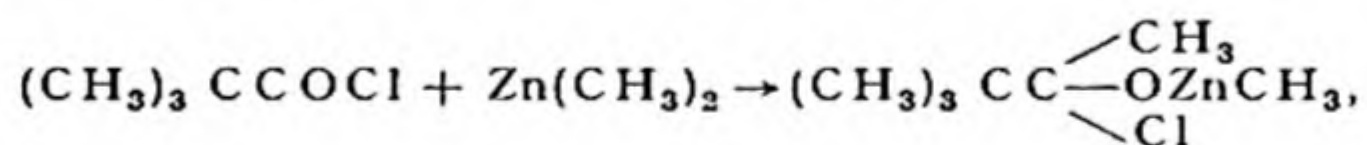


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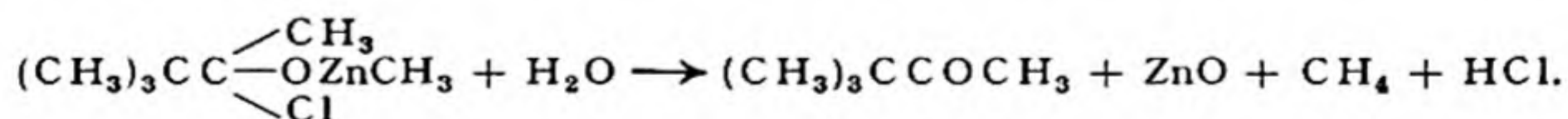
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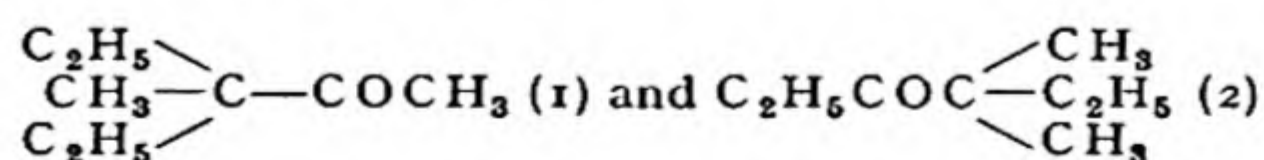
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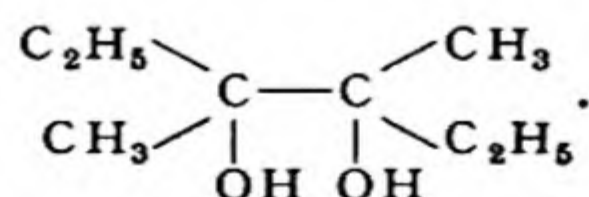
the addition product being decomposed with water:



Homologues of pinacol also may undergo a pinacolone transformation (MONTAGNE; TIFFENEAU). Thus two isomeric ketones:



may be produced from



In this case it appears that ketone (I) is the main product, from which it may be concluded that in this transformation the ethyl group is more easily displaced than the methyl group.

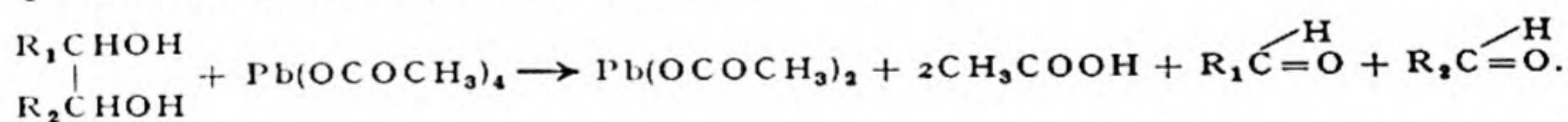
The alkanediols or glycols are usually colourless, viscous liquids with a sweet taste (hence their name). The lower members of the series are miscible with water and ethanol in all proportions but sparingly soluble in ether. The boiling points and specific gravities are higher than those of the monohydric alcohols with the same number of carbon atoms.

TABLE 31
BOILING POINTS AND SPECIFIC GRAVITIES OF SOME ALKANEDIOLS

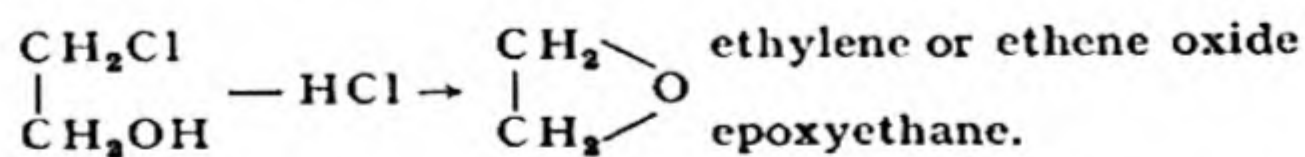
Name	Formula	Boiling point	Specific gravity
Ethane-1,2-diol	CH ₂ OHCH ₂ OH	197.37°	1.1297 at 0°
Propane-1,3-diol	CH ₂ OHCH ₂ CH ₂ OH	214°	1.0526 at 18°
Propane-1,2-diol	CH ₂ OHCH ₂ OHCH ₃	189°	1.051 at 0°
Butane-1,2-diol	CH ₂ OHCHOHCH ₂ CH ₃	194°	1.0189 at 0°
Butane-1,3-diol	CH ₂ OHCH ₂ CHOHCH ₃	207°	1.0259 at 0°
Butane-1,4-diol	CH ₂ OHCH ₂ CH ₂ CH ₂ OH	230°	1.020 at 20°
Butane-2,3-diol	CH ₃ CHOHCHOHCH ₃	180°	1.048 at 0°

III. As with monohydric alcohols the hydroxyl groups in the diols can be esterified and converted into alkoxy-groups. -CH₂OH groups in diols can be oxidised to aldehyde or acid groups. Compounds such as CH₂OHCH₂Cl, 2-chloroethanol, CH₂OC₂H₅CH₂OH, 2-ethoxyethanol, CH₂OC₂H₅CH₂OC₂H₅, 1,2-diethoxyethane, are known, for example.

Glycols in which the hydroxyl groups are situated on adjacent carbon atoms can be dehydrogenated by lead tetra-acetate with the rupture of the carbon chain and the production of aldehydes or ketones (CRIEGEE)



On account of the presence of two hydroxyl groups in the molecule the diols can form internal anhydrides. From the first member, *ethylene glycol*, *ethane-1,2-diol*, CH₂OHCH₂OH, the internal anhydride *cannot* be obtained by splitting off water directly. A compound C₂H₄O is formed, however, by splitting off hydrogen chloride from 2-chloroethanol:



The above structure is given to *ethylene* or *ethene oxide* or *epoxyethane*, since 1,2-dichloroethane is produced by the action of phosphorus pentachloride,

the oxygen atom being replaced by two chlorine atoms. With the alternative structure, which could be imagined from the method of formation but which is less probable, namely, $\text{CH}_2=\text{CHOH}$, the action of phosphorus pentachloride should lead to vinyl chloride.

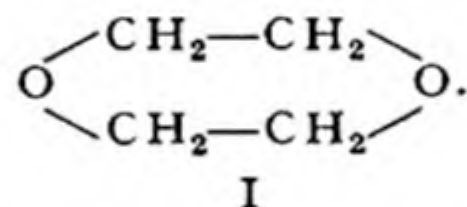
Ethene oxide (b.p. 12.5°) is converted into glycol by warming with water, while 2-chloroethanol is produced by the action of hydrogen chloride. When ethene oxide is passed over aluminium oxide at 200° it is changed into acetaldehyde with which it is isomeric.

Some homologues of glycol in which the hydroxyl groups are separated from each other by 4 or 5 carbon atoms, give anhydrides to which a similar structure to that of ethene oxide is ascribed.

In these homologues of ethene oxide the power of adding water is considerably diminished, that is, these *cyclic bonds* between carbon atoms and oxygen atoms are not so easily broken as in ethene oxide.

Glycol is prepared commercially by allowing ethene to add on hypochlorous acid and subjecting the resultant 2-chloroethanol to hydrolysis whereby the chlorine atom is replaced by a hydroxyl group. Glycol and especially its ethers and esters are used as solvents in chemical industry.

On distilling glycol with 4 % sulphuric acid there is produced along with other products, 1,4-dioxan, a cyclic ether of glycol (I):



Dioxan boils at 101° and melts at 11° . It is miscible in all proportions with water and most organic solvents. Dioxan is an excellent solvent for many organic compounds, including esters and ethers of cellulose; it is very poisonous.

(b) Trihydric alcohols

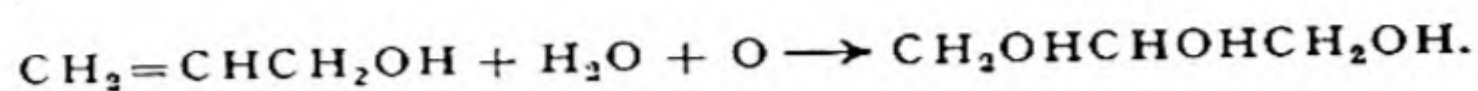
112. The most important representative of this group is propane-1,2,3-triol, $\text{C}_3\text{H}_5(\text{OH})_3$ or glycerol, which occurs naturally in fats as esters of higher fatty acids (see 114), as a constituent of phosphatides (119) and in very small quantities in blood. It is prepared commercially by saponifying fats.

The structure of glycerol, $\text{CH}_2\text{OHCHOHCH}_2\text{OH}$, is deduced as follows: by careful oxidation of $\text{C}_3\text{H}_8\text{O}_3$ there is produced a *mono-basic acid*, $\text{C}_3\text{H}_6\text{O}_4$, *glyceric acid*. Hence a $-\text{CH}_2\text{OH}$ group must be present in the glycerol molecule. By oxidising glyceric acid there is produced a *di-basic acid*, *tartronic acid*, $\text{C}_3\text{H}_4\text{O}_5$. Therefore a $-\text{CH}_2\text{OH}$ group must be present in the molecule of glyceric acid, so that two $-\text{CH}_2\text{OH}$ groups must occur in the glycerol molecule.

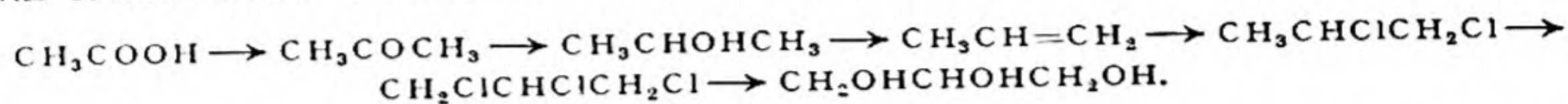
It can be proved by synthesis that the structure of tartronic acid is represented by COOHCHOHCOOH ; therefore the group $-\text{CHOH}$ must also be present in glycerol, which establishes the structure of this trihydric alcohol.

This structure is confirmed by various syntheses.

Glycerol is produced from allyl alcohol by careful oxidation with alkaline permanganate:



A synthesis of glycerol from the elements was described by FRIEDEL and DA SILVA in 1873. They started from acetic acid, which can be prepared from the elements in various ways. From this they prepared propanone, which was converted into propene via propanol-2. 1,2-Dichloropropane was obtained from propene and was converted into 1,2,3-trichloropropane by treatment with iodine chloride. Glycerol was formed when the trichloro-compound was heated with water at 170°:

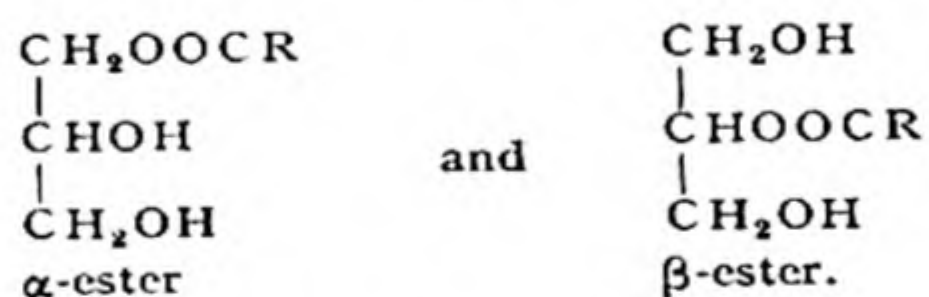


At the present time glycerol is prepared on a large scale from allyl chloride, which is obtained by chlorinating propene (81).

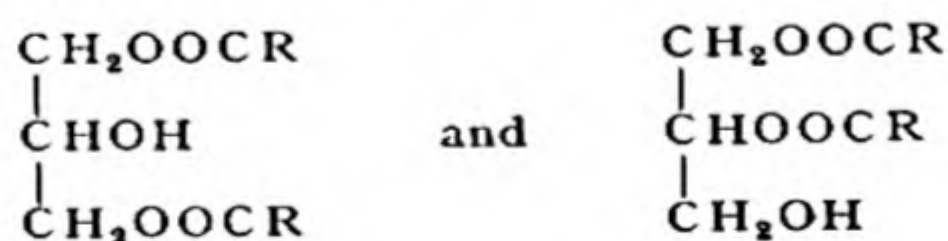
Glycerol was observed as a fission product of olive oil by SCHEELE as early as 1779. The chemical properties of this alcohol were investigated mainly by PELOUSE, BERTHELOT and WURTZ.

Glycerol is a colourless, syrupy liquid with a sweet taste; it boils at 290°. Pure glycerol crystallises on long continued cooling; it melts at 17°. Glycerol is very hygroscopic and is miscible in all proportions with water and ethanol but it is sparingly soluble in ether.

Three kinds of esters may be derived from glycerol according to whether one, two or three hydroxyl groups are esterified. Two isomeric forms are possible for the mono-esters and are known in a number of cases:

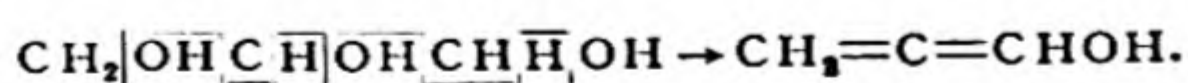


Di-esters with the same acid residues may also exist in two isomeric forms



while with dissimilar acid residues three isomers are possible.

The method of preparation of propenal mentioned in (97) by splitting off a molecule of water from glycerol, may be formulated as follows:



This hypothetical unsaturated alcohol with OH attached to a doubly bound carbon atom undergoes an isomeric change to produce its isomer propenal, $\text{CH}_2=\text{CHCHO}$.

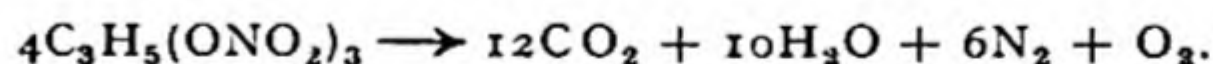
The hydrogen atoms of the hydroxyl groups in glycerol are more easily replaceable by metals than those in monohydric alcohols. When a solution of copper sulphate is added to glycerol and this is then followed by excess sodium hydroxide solution, no precipitate of copper hydroxide is produced. The solution assumes a deep blue colour and contains *sodium cupriglycerate*. This substance may be isolated in a solid state and has the composition $(\text{C}_3\text{H}_5\text{O}_3\text{CuNa})_2 \cdot 3\text{H}_2\text{O}$.

Calcium and *lead glycerates* are produced by boiling glycerol with calcium and lead oxides respectively. These compounds $\text{C}_3\text{H}_6\text{O}_3\text{Ca}$ and $\text{C}_3\text{H}_6\text{O}_3\text{Pb}$ are decomposed by boiling with water into glycerol and metal hydroxide.

Glycerol is used for very many technical purposes and also in medicine. On account of its sweet taste and its preserving properties it is added to foodstuffs and luxury products. It is used in the preparation of pharmaceutical and cosmetic preparations, in the manufacture of inks and in the finishing of textile goods.

Large quantities of glycerol are used for the preparation of glycerol trinitrate (SOBRERO, 1844): $\text{CH}_2\text{ONO}_2\text{CHONO}_2\text{CH}_2\text{ONO}_2$, the explosive known as *nitroglycerine*, an incorrect name, since this compound is an ester derived from glycerol and nitric acid; it is split up into glycerol and alkali nitrate by the action of alkalis. Nitroglycerine is obtained by treating glycerol with a mixture of nitric acid and sulphuric acid with cooling; the nitroglycerine separates as a heavy liquid when the reaction mixture is poured into water. It has a specific gravity of 1.6 and occurs in two modifications in the solid state; the metastable form melts at 2.2° and the stable form at 13.3° .

Nitroglycerine can be made to explode very violently by a blow or shock, when it decomposes according to the equation:



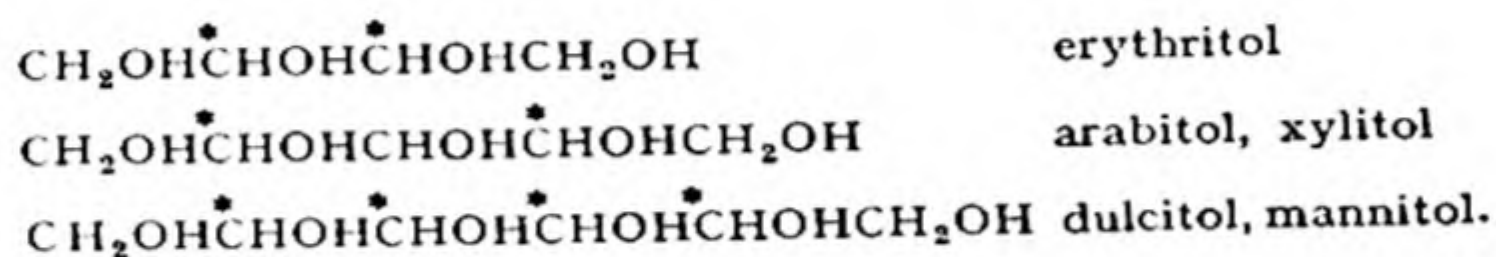
Since nitroglycerine is a liquid, it is not used as such as an explosive. When it is absorbed in infusorial earth, *dynamite* (A. NOBEL, 1866), which contains about 75 % of nitroglycerine, is obtained. Dynamite is exploded by using a small quantity of an "initiator" or "detonator" such as mercury fulminate (157) or lead azide. On account of its very high explosion rate dynamite is not used as a filling for cartridges; it has a "high explosive" action. Other explosives consisting mainly of nitroglycerine are obtained by dissolving about 7 % of nitrocellulose (190) in the liquid. In this way there is produced a solid colloidal mass, *blasting gelatine*; when exploded this substance leaves no solid residue.

(c) *Tetrahydric and higher polyhydric alcohols*

113. A tetrahydric alcohol, *butane-1,2,3,4-tetraol* or *erythritol* occurs in some algae; esters of this alcohol are met with in lichens. On heating erythritol with hydriodic acid, 2-iodobutane is produced, from which it may be concluded that erythritol has a normal carbon chain.

Arabitol and *xylitol* are two pentahydric alcohols; they are stereoisomers like the hexahydric alcohols *dulcitol* and *mannitol*. They have a normal carbon chain as is shown by heating with hydriodic acid when mono-iodoalkanes with normal chains are produced. Thus 3-iodohexane, $\text{CH}_3\text{CH}_2\text{CHICH}_2\text{CH}_2\text{CH}_3$, is produced from mannitol.

The stereochemical structure of these alcohols will be discussed in **164**. It is sufficient to say now that asymmetric carbon atoms, indicated by an asterisk in the formulae below, occur in these alcohols:



Pentahydric alcohols (pentitols) and hexahydric alcohols (hexitols) can be obtained by reduction of the corresponding aldehydes or ketones [monosaccharides (**159**)]; thus dulcitol is produced from galactose and mannitol from mannose and fructose.

d-Mannitol, melting at 166° , occurs in various plants; it is the chief constituent of manna, the dried up sap of the manna-ash (*Fraxinus ornus*). Dulcitol also occurs in the vegetable kingdom as do other stereoisomeric hexitols, such as *iditol* and *sorbitol*. These polyhydric alcohols are fairly readily soluble in water; like glycerol they readily form alcoholates with heavy metals.

Polyhydric alcohols show a characteristic behaviour towards boric acid. Boric acid is a very weak acid which shows a very small electrical conductivity in aqueous solution; however, when an equimolecular quantity of a polyhydric alcohol is added to the solution, the conductivity increases considerably. The significance of this phenomenon for the determination of structure is discussed in a subsequent paragraph (**168**).

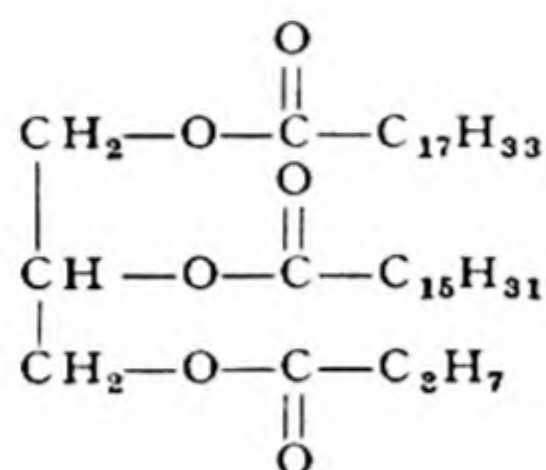
(d) *Fats*

114. The fats occurring in the vegetable and the animal kingdoms are mixtures of triglycerides. They are esters of glycerol with alkane carboxylic acids or with unsaturated acids, in which all the hydroxyl groups in the glycerol are usually esterified. Separation of the pure glycerides from fats is

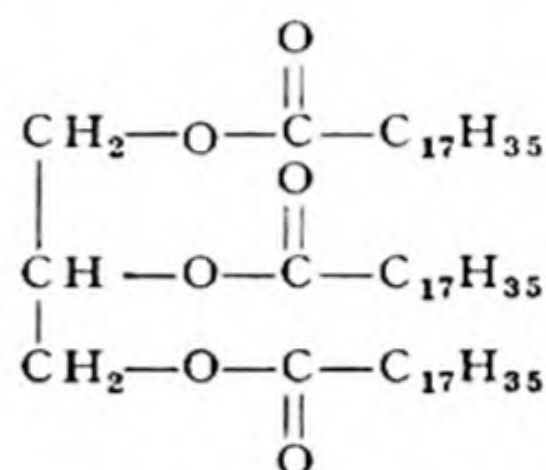
difficult, since these esters differ but slightly in solubility and they cannot be distilled without decomposition except at very low pressures.

Glyceryl 1-oleo-2-palmito-3-stearate has been isolated from lard, *glyceryl tristearate* or *tristearin* from beef tallow and *glyceryl oleo-palmito-butyrate* occurs along with other esters in butter.

A glyceride like glyceryl tristearate in which three similar acid radicals are combined, is called a *single acid triglyceride*; if three different acid radicals are present in the molecule, the compound is called a *triple acid triglyceride* and if two acid radicals are identical and a third different, the compound is then termed a *double acid triglyceride*:



Glyceryl oleo-palmito-butyrate
or α -oleyl- β -palmityl- γ -butyrylglycerol



Glyceryl tristearate.

Glyceryl tripalmitate or *tripalmitin* has also been found as a constituent of fats. *Glyceryl trioleate* or *triolein* is a constituent of olive oil.

Usually it is not possible to isolate as such, all the individual triglycerides occurring in a natural fat, but these are determined by the qualitative and quantitative examination of the mixture of fatty acids produced on hydrolysis. It is of course impossible to say what radicals are combined in the individual triglycerides. From melting point data obtained on vegetable oils and fats and pure triglycerides, the important conclusion has been reached that in vegetable organisms triple acid triglycerides are formed preferentially.

The fatty acids obtained from animal or vegetable fats, be they saturated or unsaturated acids, all have an *even* number of carbon atoms. The fatty acids obtained from so called hard fats like beef and mutton tallow, are composed chiefly of stearic acid and palmitic acid. A large proportion of oleic acid is obtained on splitting liquid fats (oils), such as olive oil or almond oil, or soft fats like lard.

Butter contains, besides 16 % of water, about 84 % of fat; all the saturated fatty acids with an even number of carbon atoms from C_4 (butyric acid) to C_{20} (arachidic acid) and sometimes still higher to C_{26} (cerotic acid) occur in its fatty acids to an extent of about 60 %. As regards unsaturated acids, the chief constituents are oleic acid and decenic acid together with a few others all of which have a double bond between the 9th and 10th carbon atoms. Butter fat is composed of triglycerides in which at least two different fatty acid radicals are usually present. When butter is

hydrolysed with aqueous caustic soda and the mixture acidified with sulphuric acid is distilled, about 2–3 % of butyric acid, caproic acid etc. passes over with the steam. These acids are therefore denoted as *volatile fatty acids*; the determination of the volatile fatty acid content is important in differentiating butter from margarine.

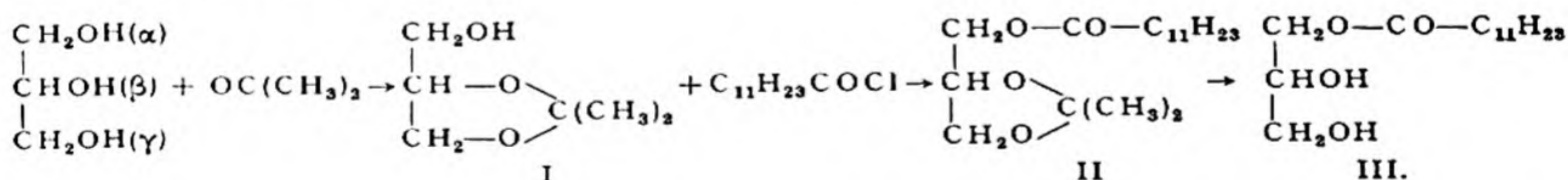
Small quantities of volatile fatty acids are also produced in the hydrolysis of cocoa-butter.

Arachidic acid ($C_{20}H_{40}O_2$) is produced by hydrolysing ground-nut or arachis oil (*arachis hypogaea*); *myristic acid* ($C_{14}H_{28}O_2$) is produced from the oil derived from nutmegs (*myristica*), *lauric acid* ($C_{12}H_{24}O_2$) from bay-oil and cocoanut oil, *behenic acid* ($C_{22}H_{44}O_2$) from rape oil and ground-nut oil.

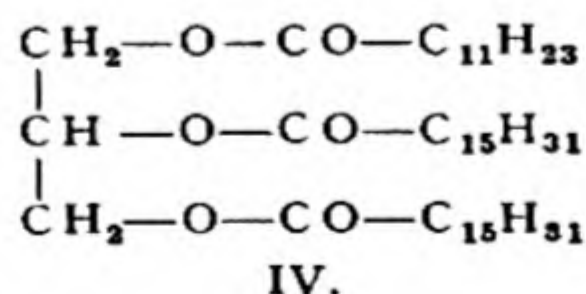
Linseed oil has the property of taking up oxygen from the atmosphere and being converted thereby into a solid, transparent mass (varnish); both oxidation and polymerisation of the linseed oil take place. Because of this property linseed oil is called a *drying oil*. Linolic acid and linolenic acid, produced by splitting linseed oil, have already been mentioned in (102). A glyceride of an unsaturated hydroxy-acid, *ricinoleic acid*, occurs in castor oil.

Synthesis of triglycerides. It is important to prepare triglycerides of known constitution, synthetically in order to be able to compare them with triglycerides isolated from natural fats. Single acid triglycerides, e.g. glyceryl tristearate, tripalmitate, tributyrates, etc., are prepared by heating glycerol with three equivalents of fatty acid under reduced pressure until no more water is produced (BERTHELOT; SCHEY).

Double acid triglycerides have been prepared by E. FISCHER. In the presence of sodium sulphate glycerol reacts with acetone with the production of compound I, which may also be regarded as a ketone-acetal. When I is treated with, for example, lauryl chloride, II is produced, from which the acetone residue may be split off by the action of dilute hydrochloric acid at low temperatures with the formation of α -laurylglycerol III:



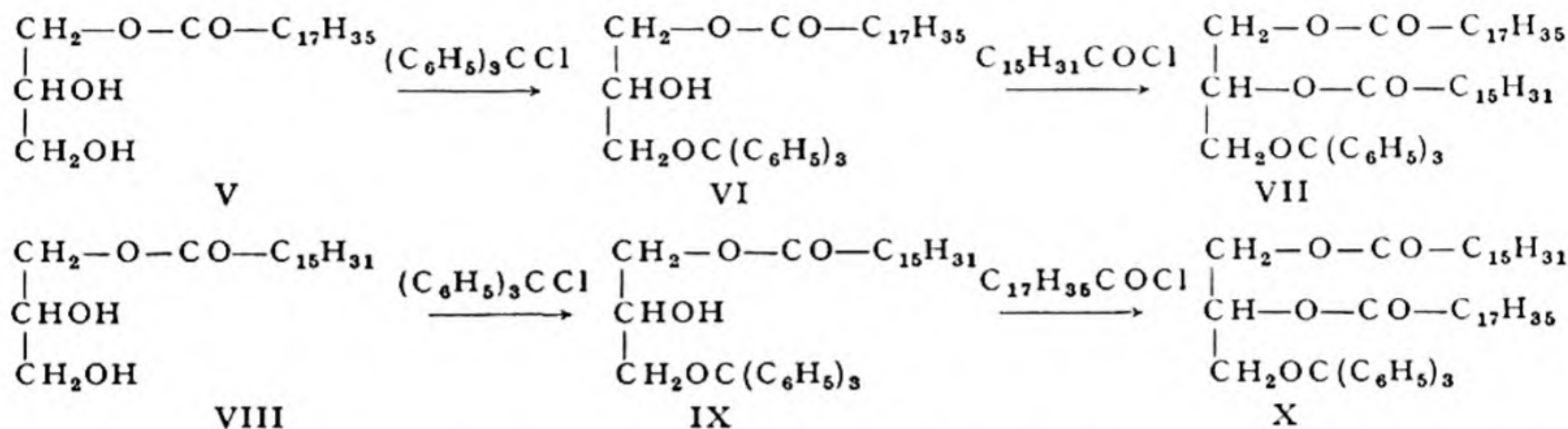
By treating III with another acid chloride, e.g. palmityl chloride, α -lauryl- $\beta\gamma$ -dipalmityl-glycerol IV is obtained:



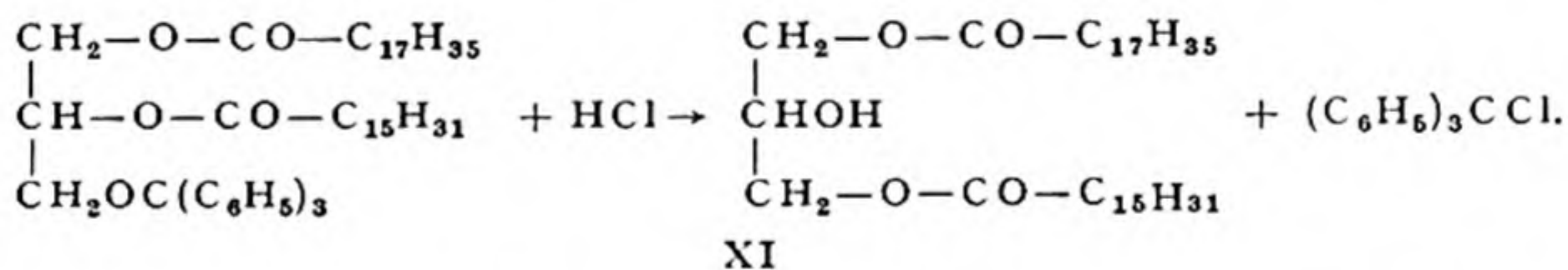
In this way double acid triglycerides with identical acyl residues in the β - and γ -positions are made available.

Methods for the synthesis of triple acid glycerides have been discovered by VERKADE. From the researches of HELFERICH it was known that polyhydric alcohols react with

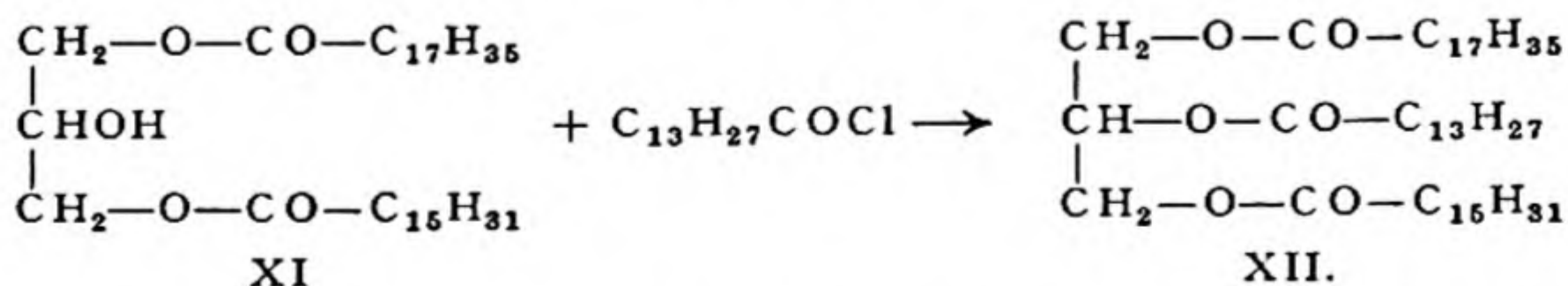
triphenylchloromethane, $(C_6H_5)_3CCl$, (273), in pyridine solution, hydrogen chloride being split off with the production of a triphenylmethyl ether. In this reaction a primary alcohol grouping reacts more rapidly than a secondary grouping. VERKADE treated α -stearyl glycerol (α -mono-stearin) V (obtained by E. FISCHER's method) with triphenylchloromethane, when compound VI was produced. This compound was now converted into compound VII (m.p. 37°) by means of palmityl chloride. When, however, he started from α -palmityl glycerol VIII, then in a similar way, via IX a compound X was obtained, which melted at 57° and was isomeric with VII. From this it follows, that by the action of triphenylchloromethane on the mono-glycerides V and VIII, the group $(C_6H_5)_3C-$ enters in the γ -position.



When compound VII is treated in light petroleum with hydrogen chloride, triphenylchloromethane separates; at the same time another reaction takes place by which the fatty acid radical attached to the β -position migrates to the γ -position, so that α -stearyl- γ -palmityl-glycerol, XI, is produced:

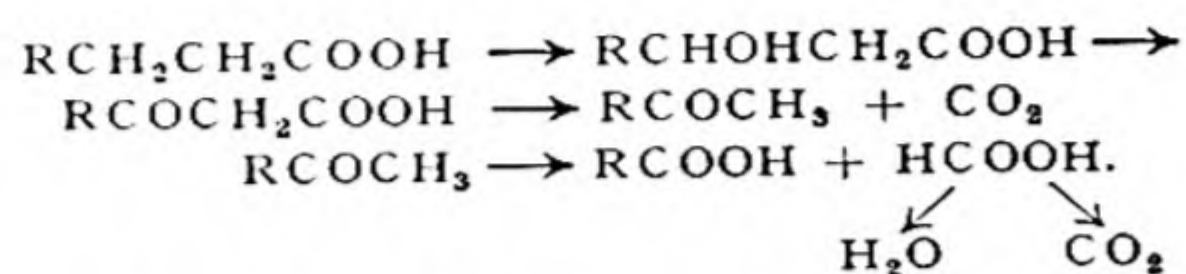


That this reaction takes the course indicated, is apparent from the fact that α -stearyl- $\beta\gamma$ -dipalmityl-glycerol, which can also be prepared by the method of E. FISCHER, is produced by the action of palmityl chloride on XI. Compound XI is converted by the action of myristyl chloride into α -stearyl- β -myristyl- γ -palmityl-glycerol, XII, which melts at $59.5-60^\circ$. In a similar way VERKADE obtained α -stearyl- β -palmityl- γ -myristyl-glycerol (m.p. $58-59^\circ$). It is noteworthy that the melting points of these isomeric triglycerides differ so slightly:



Fats form an important constituent of the food of man and animals; during digestion the fats are split up into glycerol and fatty acids by the action of enzymes, called *lipases*, which are secreted by the pancreatic gland. The fats are built up afresh in the body from these fission products.

Part of the fatty acids are consumed in the body and so liberate energy. In this "combustion" it is assumed that carbon atom 2 is first oxidised; the β -ketonic acid so produced, easily loses carbon dioxide with the formation of a ketone, which is degraded further by subsequent oxidation (KNOOP). The reaction scheme for this β -oxidation is as follows:



Thus each time, an acid is produced having two carbon atoms less than its precursor. Propanone carboxylic acid or acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$ (147) which is produced in this degradation is oxidised further in the normal organism; in sufferers from diabetes, however, this compound is split up into acetone and carbon dioxide.

From researches carried out by VERKADE it appears that fatty acids can be broken down in the human body, in another way, so that a terminal methyl group is oxidised and acids of the type $\text{HOOC}(\text{CH}_2)_n\text{COOH}$ are produced (ω -oxidation).

115. Technical applications of fats. Fats serve as the starting material for very important industries such as the manufacture of soap, margarine and similar edible fat products, glycerol and tallow candles.

For the preparation of margarine, solid fats of animal or vegetable origin are melted and mixed with the necessary quantity of soft fats or oils and the mixture churned with milk. The margarine is separated from the resultant emulsion by cooling.

For the preparation of soap, fats (tallow, palm-oil, cocoanut oil), are split by heating with caustic soda or caustic potash (*soap boiling*), by which the sodium or potassium salts of the fatty acids are produced along with glycerol. In order to prepare hard soaps (toilet soaps) common salt is added to the hot liquid (salting out), when the sodium salts of palmitic acid and stearic acid separate on the top of the liquid which contains the glycerol, because these salts are insoluble in a concentrated solution of common salt. The soap obtained in this way is called *grain soap*, it consists of the sodium salts of the above mentioned acids together with a few per cent of water. Soaps are also prepared from palm kernel oil and cocoanut oil in which the sodium salts of the fatty acids are not separated from the water and the glycerol by salting, but the whole mass is allowed to set. Thus the soap obtained in this way ("filled soap") contains also glycerol and water. The potassium salts of these fatty acids are soft; along with glycerol and water they form the constituents of the *soft soaps*, which are used extensively in the textile industries and in the household.

A soap solution is to be regarded as a sol of a hydrophylic colloid, which shows surface activity. The characteristic of this is, that the molecules of the dissolved substance are not completely equally divided throughout the solution in which they are situated, but accumulate in the surfaces and lower their surface tension (*e.g.* air-water, oil-water, textile-water). On account of this lowering of the surface tension the solution penetrates much more easily into capillary spaces than does pure water. Accumulation on the surfaces of substances such as textiles and dirt (clay, soot, fatty substances, etc.) is enhanced by a certain affinity of these surfaces for ionised soap molecules. This is called adsorption and the manner in which this adsorption takes place causes a repulsion between the textile material and foreign matter and dirt particles. By so doing the soap exerts a cleaning action on the textile material and a dispersing action on the contaminants in the suds.

Further, the state of the soap molecules in solution is important in connection with detergent action. According to researches by McBAIN, HARTLEY and others, there exists in the solution an equilibrium between ionised and undissociated soap molecules and conglomerates of molecules, which in their turn are partly ionised, the so called soap micelles. These soap micelles probably play a part in emulsifying liquid dirt like vegetable or mineral oil.

When the sodium salts of the fatty acids with decreasing numbers of carbon atoms are mutually compared with regard to the properties mentioned above, it is seen that the latter gradually disappear but not all simultaneously. First of all the power of adsorption on solid surfaces is lost, then the power of forming micelles and finally the surfaceactive properties disappear. Parallel with this is observed the loss of detergent properties for solid substances, a similar loss for oil and a simultaneous loss of emulsifying power and lowering of the surface tension.

When fats are heated with water under pressure to about 170° with the addition of very small quantities of zinc oxide or lime, hydrolysis occurs under the influence of hydroxyl ions present, with the formation of glycerol and free fatty acids. Another method of fission depends on the fat-splitting action of an enzyme present in castor seed; the fat is ground up with shelled, oil-free seeds and emulsified with water. Hydrolysis takes place in a weakly acid medium at $30-40^{\circ}$.

Hydrolysis also takes place rapidly at 100° when a mixture of fat and water is heated with a mixture of sulphonic acids obtained by sulphonating oleic acid and naphthalene (TWITCHELL's method).

In these methods glycerol and free fatty acids are obtained. The glycerol is purified by distillation. The mixture of fatty acids is soft at ordinary temperatures; after pressing out the liquid oleic acid, a white, solid mass remains behind, which consists of stearic and palmitic acids and is used in the manufacture of *tallow candles*.

The soap and margarine industries consume large quantities of solid fats; solid fats of animal and vegetable origin are available, however, in smaller quantities than liquid and soft fats, which consist mainly of glycerides of oleic, linolic and linolenic acids. These unsaturated fats are converted into saturated fats, having higher melting points, by adding finely divided nickel to the oil and treating the well stirred mixture with hydrogen under pressure at about 180° , when the hydrogen adds on to the double bonds under the catalytic action of the nickel. This process of "*fat hardening*", discovered by NORMANN (1902), is of great technical importance.

Fats may become rancid; this is caused by slow oxidation by atmospheric oxygen accelerated possibly by light. Heptanal, which gives rise to the rancid odour, can be produced from the carbon skeleton of oleic acid. Also hydrolysis by water with the production of free fatty acids can take place under the influence of micro-organisms or fat-splitting enzymes (205), *e.g.* the unpleasant smelling butyric acid is produced in butter. The free fatty acids are broken down oxidatively under the influence of micro-organisms with the production of ketones, *e.g.* methyl heptyl ketone from capric acid (β -oxidation).

(iii) POLY-SUBSTITUTED COMPOUNDS CONTAINING HALOGEN ATOMS, HYDROXYL-, NITRO- OR AMINO-GROUPS

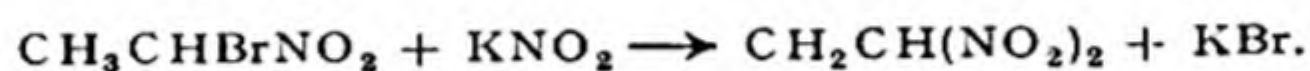
116. Only a few of the numerous compounds which should be included in this chapter, will be discussed.

Halogeno-alcohols. 2-Chloroethanol, $\text{ClCH}_2\text{CH}_2\text{OH}$, is prepared by the action of hydrogen chloride on glycol. This reaction can be carried out in such a way that only one hydroxyl group is replaced by chlorine. This alcohol is also prepared by the addition of hypochlorous acid to ethene (85). Chloroethanol is used in various syntheses.

Tribromoethanol, $\text{CBr}_3\text{CH}_2\text{OH}$, has a powerful hypnotic action and is used for this purpose in medicine under the name of *Avertin*.

1,3-Dichloropropanol-2, $\text{CH}_2\text{ClCHOHCH}_2\text{Cl}$, is obtained by the action of hydrogen chloride dissolved in glacial acetic acid on glycerol. The dichloropropanol obtained in this way differs from the dichloropropanol, $\text{CH}_2\text{OHCHClCH}_2\text{Cl}$, produced by the addition of chlorine to allyl alcohol; this fact establishes its structure.

Nitro-compounds. *Dinitroalkanes* with the two nitro-groups on the same carbon atom can be obtained by allowing potassium nitrite to react on primary bromonitro-compounds:

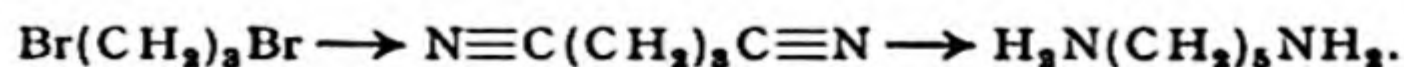


The hydrogen atom which is attached to the carbon atom carrying the nitro-groups, is very easily replaceable by metals. These dinitro-compounds have acid properties.

Tetranitromethane, $\text{C}(\text{NO}_2)_4$, (m.p. 13° , b.p. 126°) is produced, for example, by the action of very concentrated nitric acid on acetic anhydride. It gives coloured addition compounds with many unsaturated hydrocarbons; therefore this substance is a sensitive reagent for the presence of alkenes in mixtures of hydrocarbons.

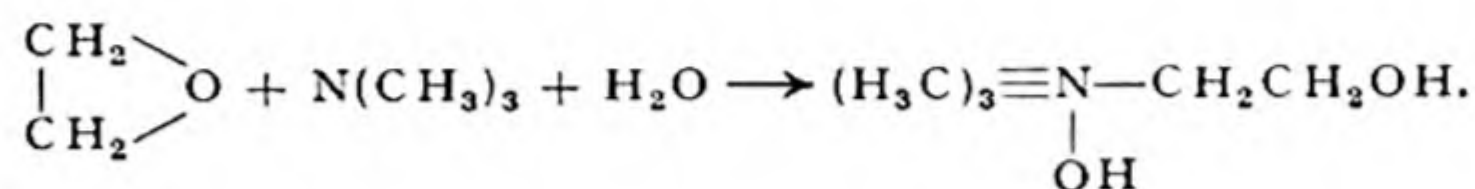
117. Diamines. Diamines with two amino-groups on the same carbon atom are known only in the form of their derivatives. Diamines with amino-groups on different carbon atoms can be obtained, for example, by the action of ammonia on dihalogenoalkanes.

1,4-Diaminobutane, $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ or *putrescine* and *1,5-diaminopentane*, $\text{H}_2\text{N}(\text{CH}_2)_5\text{NH}_2$, or *cadaverine* are produced by the decomposition of proteins by micro-organisms, *e.g.* in putrifying meat. These substances, also called *ptomaines*, are very poisonous; other poisonous substances (*toxins*) of unknown chemical structure are also produced by the decomposition of proteins by bacteria. The structure of the diamines follows from their synthesis, that for 1,5-diaminopentane being carried out as follows. 1,3-Dibromopropane is converted into 1,3-propane dicyanonitrile by treatment with potassium cyanide. This substance is then reduced with sodium in boiling alcohol, whereby the $-\text{C}\equiv\text{N}$ -groups are converted into $-\text{CH}_2\text{NH}_2$ -groups:



On heating 1,5-diaminopentane hydrochloride a molecule of ammonium chloride is split off and *piperidine* (332) hydrochloride is produced.

118. Aminoalcohols. *2-Aminoethanol-1* or *ethanolamine*, $\text{CH}_2\text{OHCH}_2\text{NH}_2$, can be obtained from ethene oxide and ammonia. It is a viscous liquid (b.p. 171°) miscible in all proportions with water. *Choline*, a substance which is very widely distributed in the animal and vegetable kingdoms, is an important derivative of aminoethanol. The structure of choline follows from its synthesis from ethene oxide and trimethylamine in aqueous solution:



Choline is a very hygroscopic, basic substance, which forms well crystallised salts. An acetyl derivative of choline, *acetylcholine*, occurs in ergot and also in the animal organism (muscle). This substance causes a powerful lowering of the blood pressure and contraction of the muscles.

On boiling choline with baryta water, a molecule of water is split off and *neurine*, $(\text{CH}_3)_3\text{N}-\text{CH}=\text{CH}_2$, is produced.



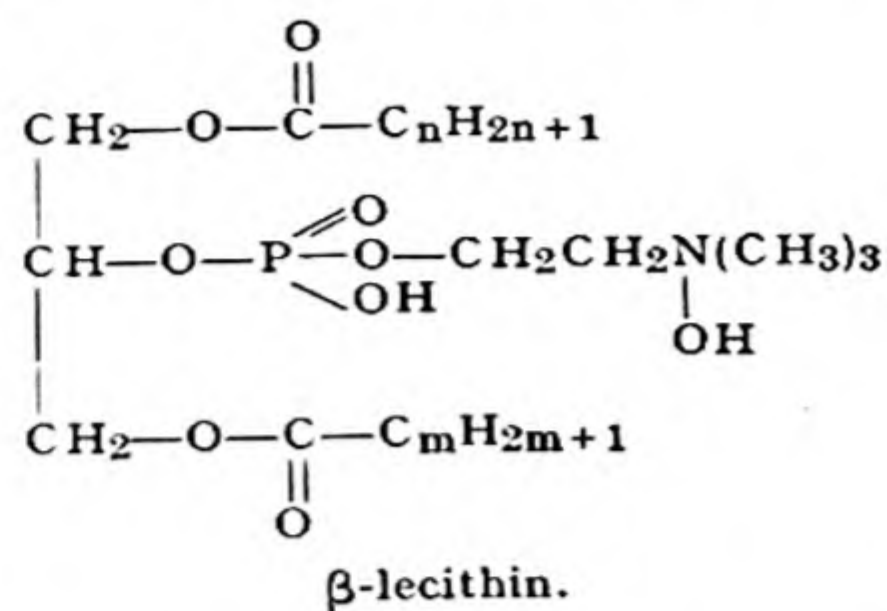
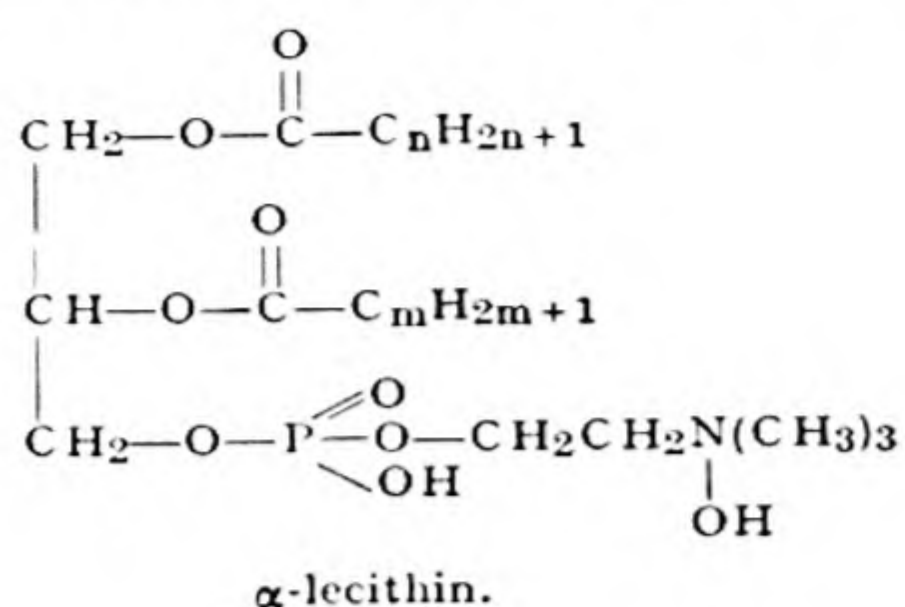
When moist silver oxide is allowed to react with the addition product $(\text{CH}_3)_3\text{NCH}_2\text{CH}_2\text{Br}$, $\begin{array}{c} | \\ \text{Br} \end{array}$ from ethylene dibromide and trimethylamine, the bromine atom attached to nitrogen is replaced by $-\text{OH}$ and at the same time HBr is split off from the $-\text{CH}_2\text{CH}_2\text{Br}$ -group to produce a vinyl group. The compound so obtained is identical with neurine. Neurine is a very poisonous substance, which is produced in putrifying flesh.

119. Phosphatides. The phosphatides form a physiologically very important group of compounds spread throughout the animal and vegetable kingdoms. The name of these compounds already indicates that they contain phosphorus. Of the phosphatides the lecithin group has been most completely investigated. The *lecithins* are very hygroscopic, waxy substances, soluble in alcohol, ether and chloroform. They form a constituent of nerve fibre especially in the brain, and of egg yolk, hence the name ($\lambda\epsilon\chi\iota\theta\omicron\sigma$ = egg yolk).

Lecithin can be isolated also from many vegetable seeds.

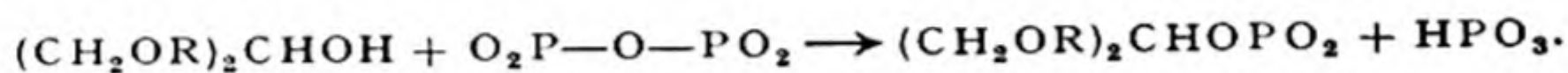
On hydrolysis, lecithins are split up into two molecules of a fatty acid (palmitic acid, stearic acid or oleic acid), a molecule of phosphoric acid, a molecule of glycerol and a molecule of choline. On careful hydrolysis with baryta water, a phosphate ester of glycerol is produced along with choline and the fatty acids mentioned above. Thus lecithins are to be regarded as esters of glycerol in which two hydroxyl groups are esterified with fatty acids and the third hydroxyl group with phosphoric acid.

One of the other hydroxyl groups in the phosphoric acid is esterified with the amino-alcohol (choline). α - and β -lecithins, derived respectively from α - and β -phosphate esters of glycerol, may be distinguished. The lecithins are represented by the following formulae:



Lecithins occurring in nature are mixtures in which β -lecithins greatly predominate. Lecithins are optically active. The middle carbon atom in the glycerol residue is asymmetric in the α -lecithins; this carbon atom is again asymmetric in β -lecithins when the fatty acid radicals are dissimilar as is assumed in the above formulae. Lecithins can give salts with both acids and bases as is shown by the structural formulae.

Lecithins are prepared synthetically in the following way. Glycerol distearate, for example, is treated with phosphorus pentoxide, when an ester of metaphosphoric acid is produced along with the acid itself:

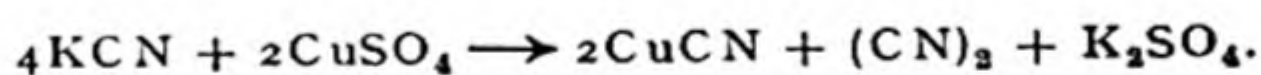


The metaphosphate ester is converted into the phosphate $(\text{CH}_2\text{OR})_2\text{CHOP}_2\text{O}_2$ on treating with water and lecithin is produced by treating this phosphate ester with aminoethanol.

Another phosphatide, *cephalin*, a constituent of the brain, is closely related to the lecithins. On hydrolysing cephalin, *serine*, $\text{HOCH}_2\text{CH}(\text{NH}_2)\text{COOH}$, (199) is produced as well as phosphoric acid and fatty acids. Since ethanolamine is readily produced from serine by splitting off carbon dioxide, this amino-alcohol has also been detected amongst the fission products from cephalin.

(iv) DICYANOGEN

120. *Dicyanogen*, C_2N_2 , is prepared by heating solutions of copper sulphate and potassium cyanide to produce cuprous cyanide and gaseous dicyanogen, since cupric cyanide, formed initially, is unstable:



This substance can also be obtained by heating mercuric cyanide, $\text{Hg}(\text{CN})_2$, (GAY LUSSAC, 1815); besides mercury and dicyanogen there is also produced a brown, amorphous polymer, paracyanogen $(\text{CN})_x$, which is split up into dicyanogen on heating to 900° .

Dicyanogen is also formed by heating ammonium oxalate with a dehydrating agent (P_2O_5) (122), when dissolved in concentrated sulphuric acid it is converted into oxamide by taking up two molecules of water. On the basis of these reactions dicyanogen must be considered as the carbonitrile 56 of oxalic acid; the structure is therefore $\text{N}\equiv\text{C}-\text{C}\equiv\text{N}$. Dicyanogen is a gas

with an irritating odour and is very poisonous; b.p. -20.7° , f.p. -27.9° ; critical temperature 128.3° , critical pressure 59.6 atmospheres. It is soluble in water; after standing for some time the solution deposits amorphous flocks of *azulmic acid*. When burnt the gas gives a reddish purple flame; at a red heat it is slowly decomposed into carbon and nitrogen. Dicyanogen is an endothermic compound; the heat of formation from the elements is -73 kcal.

Dicyanogen shows a similarity to the halogens as the following points indicate. Potassium takes fire in dicyanogen with the formation of potassium cyanide. When dicyanogen is passed into caustic potash solution, KCN and KCNO (55), are produced in the same way that KCl and KClO are formed when chlorine is passed into caustic potash. Like silver chloride, silver cyanide is insoluble in water and dilute acids but soluble in ammonia. Dicyanogen is slowly reduced to hydrocyanic acid by sulphur dioxide, like halogens are reduced to hydrogen halides. The latter reaction, however, takes place very rapidly.

(v) POLYBASIC ACIDS

(a) Saturated dibasic acids $C_nH_{2n-2}O_4$. The oxalic acid series

121. Various isomers are possible in the case of a dibasic acid of the formula $C_nH_{2n}(COOH)_2$, since the carboxyl groups may be attached in different positions in the carbon chain.

The acids in which the carboxyl groups are attached at the ends of the chain, *i.e.* of the type $COOH(CH_2)_nCOOH$, are of importance in several ways and will be discussed in the following paragraphs.

Dibasic acids can be obtained by oxidising alkanediols with terminal hydroxyl groups or by hydrolysing alkane dicyanitriles. For other methods of preparation see (123).

Some physical properties of a number of acids in this

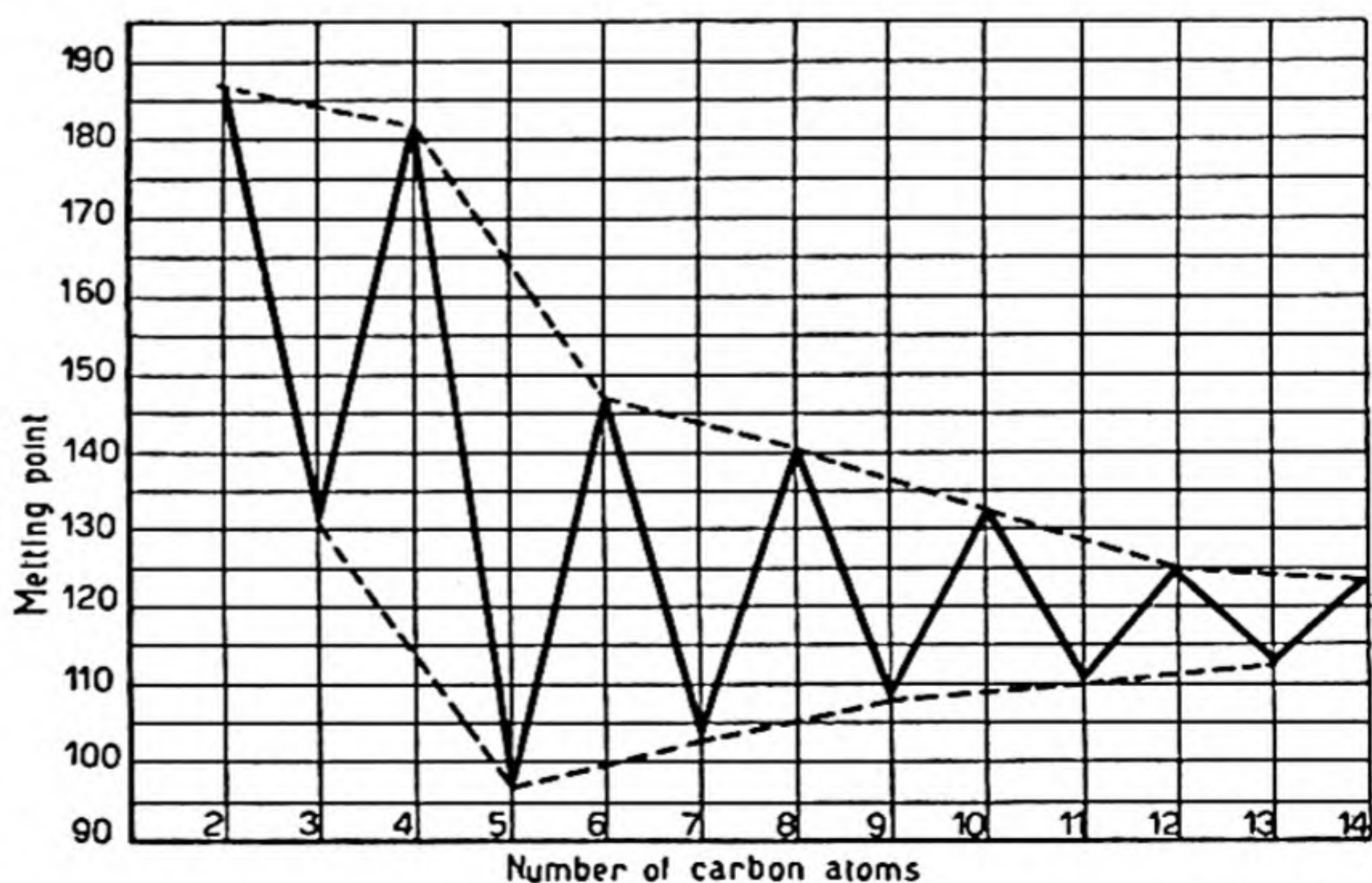


Fig. 29. Graphical representation of the melting points of the dibasic acids $C_nH_{2n-2}O_4$

TABLE 32

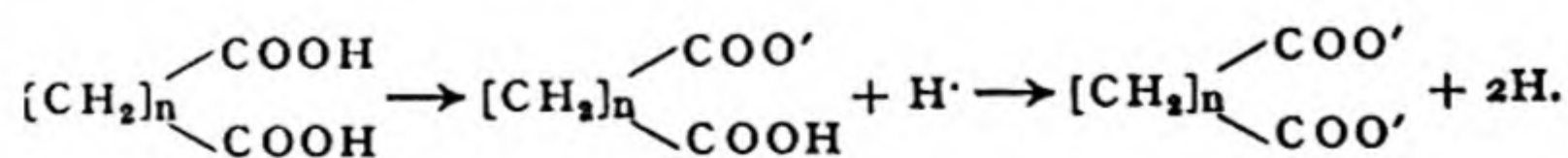
SOME PHYSICAL CONSTANTS OF SATURATED DIBASIC ACIDS

Name		Formula	M.p.	Solubility in 100 parts of water at 20°	Dissociation const.
	Oxalic acid	CO ₂ HCO ₂ H	190°	8.6	± 0.1
Methane dicarboxylic acid	Malonic acid	CO ₂ HCH ₂ CO ₂ H	133°	73.5	0.00163
Ethane 1,2-dicarboxylic acid	Succinic acid	CO ₂ H(CH ₂) ₂ CO ₂ H	187°	6.84	0.000065
Propane 1,3-dicarboxylic acid	Glutaric acid	CO ₂ H(CH ₂) ₃ CO ₂ H	98°	63.9	0.000047
Butane 1,4-dicarboxylic acid	Adipic acid	CO ₂ H(CH ₂) ₄ CO ₂ H	153°	1.5	0.000038
Pentane 1,5-dicarboxylic acid	Pimelic acid	CO ₂ H(CH ₂) ₅ CO ₂ H	106°	5.0	0.000032
Hexane 1,6-dicarboxylic acid	Suberic acid	CO ₂ H(CH ₂) ₆ CO ₂ H	144°	0.16	0.000030
Heptane 1,7-dicarboxylic acid	Azelaic acid	CO ₂ H(CH ₂) ₇ CO ₂ H	108°	0.24	0.000029
Octane 1,8-dicarboxylic acid	Sebacic acid	CO ₂ H(CH ₂) ₈ CO ₂ H	134°	0.10	0.000028
Nonane 1,9-dicarboxylic acid		CO ₂ H(CH ₂) ₉ CO ₂ H	110°	0.014	
Decane 1,10-dicarboxylic acid		CO ₂ H(CH ₂) ₁₀ CO ₂ H	127°	0.005 at 23°	
Undecane 1,11-dicarboxylic acid	Brassilic acid	CO ₂ H(CH ₂) ₁₁ CO ₂ H	113°	0.004 at 24°	
Dodecane 1,12-dicarboxylic acid		CO ₂ H(CH ₂) ₁₂ CO ₂ H	126°		
Tridecane 1,13-dicarboxylic acid		CO ₂ H(CH ₂) ₁₃ CO ₂ H	114°		
Tetradecane 1,14-dicarboxylic acid		CO ₂ H(CH ₂) ₁₄ CO ₂ H	124°		
Pentadecane 1,15-dicarboxylic acid		CO ₂ H(CH ₂) ₁₅ CO ₂ H	132°		
Hexadecane 1,16-dicarboxylic acid		CO ₂ H(CH ₂) ₁₆ CO ₂ H	118°		
Heptadecane 1,17-dicarboxylic acid		CO ₂ H(CH ₂) ₁₇ CO ₂ H	120°		

series are collected together in Table 32. Each member with an even number of carbon atoms has a higher melting point than the preceding or the succeeding member with an odd number of carbon atoms. The solubility in water is much greater for the odd members than for the even members and decreases with an increase in the number of carbon atoms. The melting points of the even and odd members approach one another more and more as the number of carbon atoms increases (see Fig. 29, p. 191).

Such differences (oscillations) in the numerical value of a physical constant for the even and the odd members of a homologous series, are found only in properties relating to the solid state and probably are connected with the crystalline form. Definite oscillations are found in the heats of combustion of the solid dibasic acids but not in the heats of combustion of the liquid dimethyl esters of these acids or in other physical properties of these liquids such as boiling point, refractive index or specific gravity.

Electrolytic dissociation of the dibasic acids takes place in two stages:

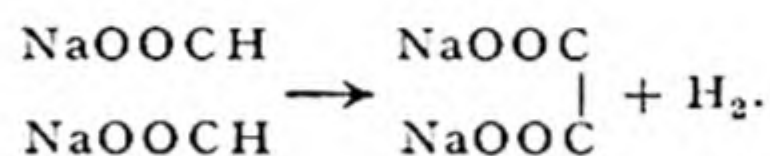


The dissociation constants for the first stage are given in table 32.

Oxalic acid is a much stronger acid than its homologues; the dissociation constants become smaller as the carboxyl groups become situated farther apart but remain of the same order of magnitude from succinic acid onwards. The dibasic acids are considerably stronger than the monobasic acids with the same number of carbon atoms.

122. Oxalic acid, dicarboxylic acid. Salts of oxalic acid occur in many plants; SCHEELE isolated oxalic acid from vegetable material as long ago as 1784. *Oxalis* (wood-sorrel) and *rumex* (dock) species contain acid potassium oxalate; calcium oxalate occurs for example in ferns, lichens and algae. Sodium oxalate can be formed by heating sodium in a stream of carbon dioxide to about 360° (KOLBE). Oxalic acid is produced by the hydrolysis of dicyanogen $\text{N}\equiv\text{C}-\text{C}\equiv\text{N}$ (WÖHLER, see 120). These methods of formation are of theoretical or historical interest.

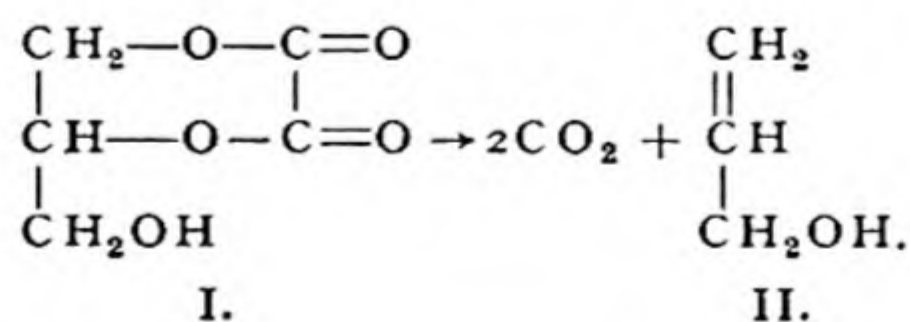
On a commercial scale sodium oxalate is prepared by rapidly heating sodium (or potassium) formate to about 360° , when hydrogen escapes from the molten mass:



Potassium oxalate is formed by heating sawdust with molten potassium hydroxide, potassium formate being produced as an intermediate product in this case also. Oxalic acid is frequently produced as a degradation product in the oxidation of organic compounds with nitric acid.

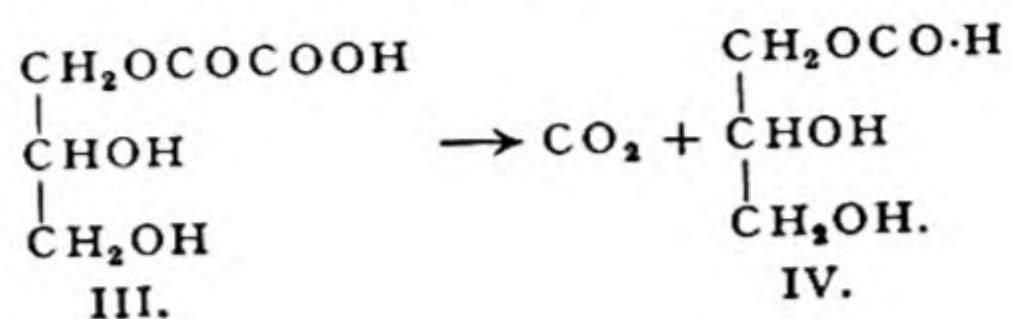
Oxalic acid crystallises with two molecules of water of crystallisation $\text{C}_2\text{H}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$. The anhydrous acid can be sublimed by careful heating but on stronger heating it decomposes to a small extent into carbon dioxide and formic acid and to a greater extent into water, carbon dioxide and carbon monoxide. The anhydride of oxalic acid is unknown.

Depending on the experimental conditions, either formic acid (see 69) or allyl alcohol (95) is formed by the action of oxalic acid on glycerol. When anhydrous oxalic acid is dissolved in glycerol at about 50° an oxalic ester, I, is formed as can be demonstrated by the production of oxamide with alcoholic ammonia. On heating to a higher temperature, carbon dioxide is split off and allyl alcohol, II, is produced:

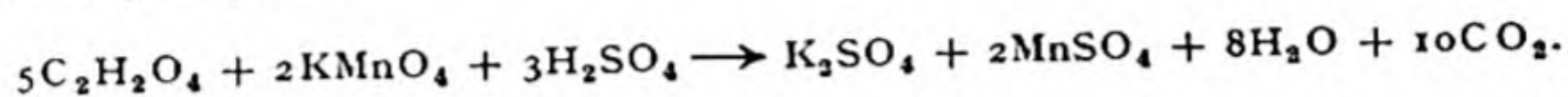


If oxalic acid containing water of crystallisation is used in this experiment, the acid oxalic ester of glycerol, III, is formed as the main product, which loses carbon dioxide on warming and is converted into the monoformate, IV. If more water-

containing oxalic acid is now added, this ester is split hydrolytically and the volatile formic acid distils over. More glycerol monoformin can now be formed so that a limited quantity of glycerol can be used to convert much more than the equivalent quantity of oxalic acid into formic acid, because glycerol is constantly regenerated:



Oxalic acid is easily oxidised by potassium permanganate in dilute sulphuric acid solution (application in quantitative analysis) according to the following equation:

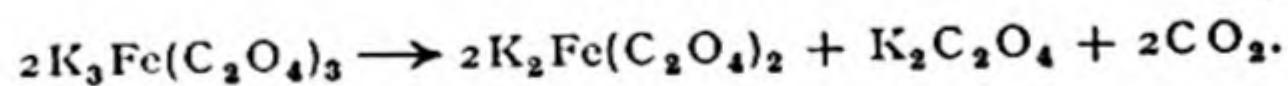


The manganese sulphate exerts a catalytic accelerating effect on this oxidation, so that the reaction takes place very rapidly as soon as a little MnSO_4 is formed.

The alkali salts of oxalic acid are readily soluble in water. The *calcium salt* $\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$, is sparingly soluble in water and in weak acids and serves as a test both for calcium and for oxalic acid. "*Salt of sorrel*", $\text{KHC}_2\text{O}_4 \cdot \text{C}_2\text{H}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$, a compound formed from a molecule of the acid potassium salt, a molecule of oxalic acid and two molecules of water of crystallisation, is an example of a *tetraoxalate*.

Very many complex salts of oxalic acid are known. *Potassium ferrous oxalate* $\text{K}_2\text{Fe}(\text{C}_2\text{O}_4)_2$ is pale yellow coloured in solution.

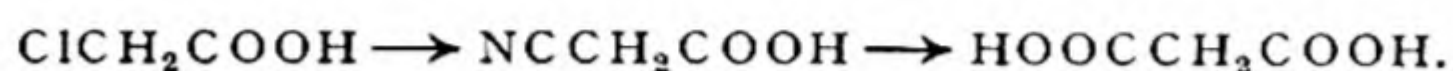
The solution therefore contains a complex anion, probably $[\text{Fe}(\text{C}_2\text{O}_4)_2]^-$, since ferrous ions have a pale green colour. This salt has powerful reducing properties and is used as a photographic developer. *Potassium ferric oxalate*, $\text{K}_3\text{Fe}(\text{C}_2\text{O}_4)_3$, dissolves in water with a green colour; the solution probably contains the complex ion $[\text{Fe}(\text{C}_2\text{O}_4)_3]^{3-}$. This solution is quickly decomposed by sunlight giving potassium ferrous oxalate:



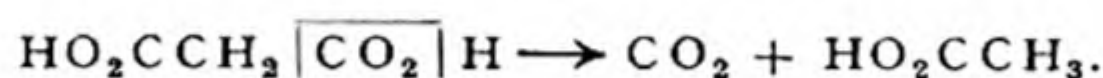
Use is made of this reaction in the manufacture of "photographic platinum prints," since potassium ferrous oxalate precipitates metallic platinum from a solution of platinum salt.

Amongst derivatives of oxalic acid may be mentioned *oxalyl chloride*, $\text{ClOC}\cdot\text{COCl}$, b.p. 64° , m.p. -12° , which may be obtained by the interaction of two molecules of phosphorus pentachloride and one of oxalic acid, and the diamide of oxalic acid, *oxamide*, $\text{H}_2\text{N}-\text{CO}-\text{CO}-\text{NH}_2$, which is produced by the action of ammonia on diethyl oxalate. Oxamide is a colourless solid, practically insoluble in water, alcohol or ether, which is remarkable, because formamide and acetamide are readily soluble in water.

123. *Methane dicarboxylic acid, malonic acid*, $\text{HO}_2\text{CCH}_2\text{CO}_2\text{H}$. The structure of this acid is apparent from its synthesis. When an alkali salt of monochloroacetic acid (**129**) is warmed in aqueous solution with potassium cyanide, *cyanoacetic acid* or *cyanomethane carboxylic acid* is produced and this is converted into malonic acid by hydrolysing the nitrile group:

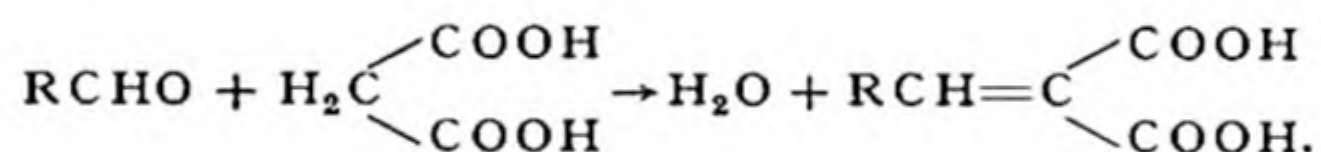


Small quantities of malonic acid occur in sugar-beet. When malonic acid is heated above its melting point, a molecule of carbon dioxide is split off with the formation of acetic acid:

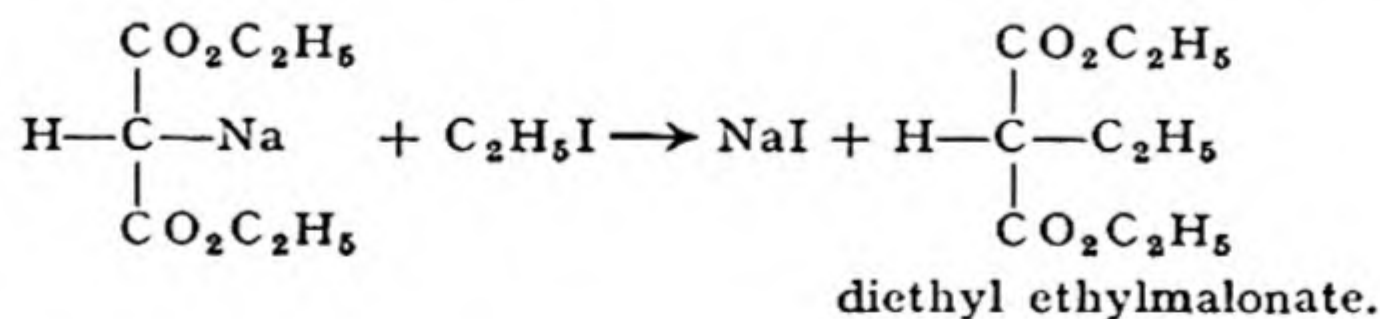


Experience has shown, that in general, acids in which two carboxyl groups are attached to one carbon atom, lose a molecule of carbon dioxide when heated above the melting point.

The two hydrogen atoms on the CH_2 -group in malonic acid are reactive; this must be ascribed to the influence of the carboxyl groups. Thus malonic acid dissolved in glacial acetic acid can react with aldehydes with the elimination of water:



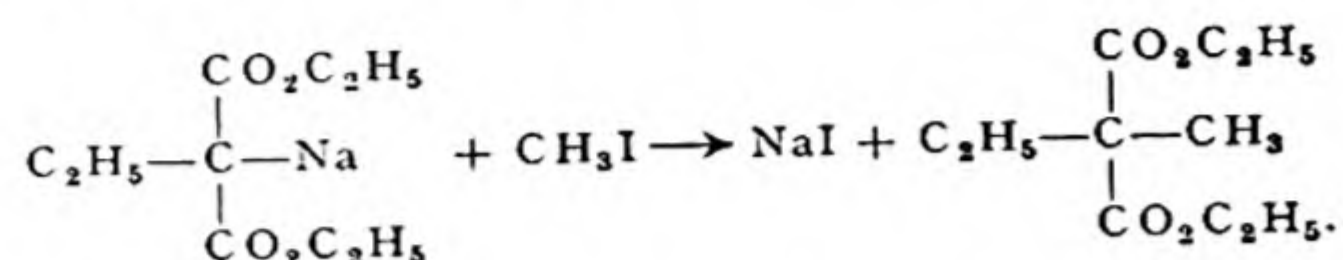
The reactivity of the hydrogen atoms of the CH_2 -group is particularly apparent from the properties of ethyl malonate. When a gram atom of sodium is introduced into a molecule of the diethyl ester, a liquid boiling at 198° , hydrogen is evolved and a solid compound, sodium ethyl malonate, $\text{H}_5\text{C}_2\text{O}_2\text{CCHNaCO}_2\text{C}_2\text{H}_5$, is formed, in which an atom of hydrogen is replaced by sodium. The structure of this sodium compound is apparent from the action of an alkyl iodide which results in the production of sodium iodide and an ester, which gives a homologue of malonic acid on hydrolysis, *e.g.*:



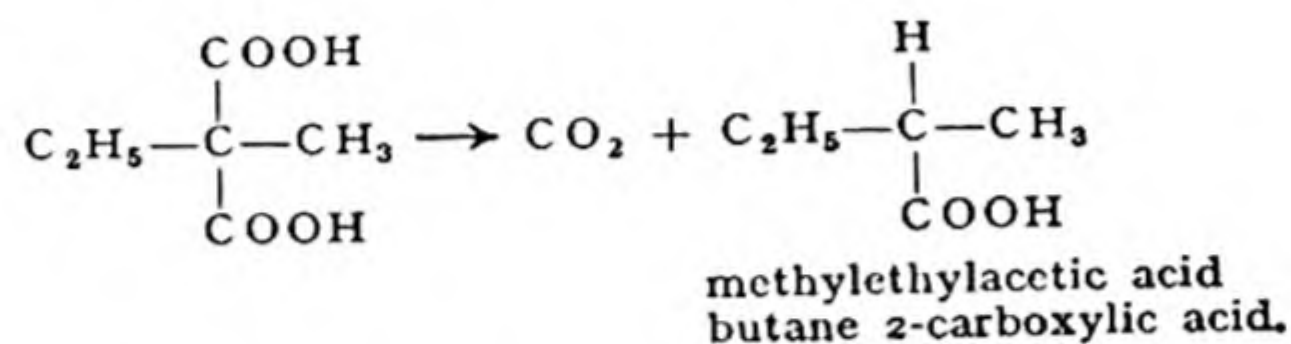
The homologues of malonic acid obtained in this way, split off a molecule of carbon dioxide on heating and pass over into alkane carboxylic acids; thus in the above example *n*-butyric acid is produced.

This method of synthesis, called the *malonic ester synthesis*, can be extended as follows. The diethyl ester of ethylmalonic acid mentioned

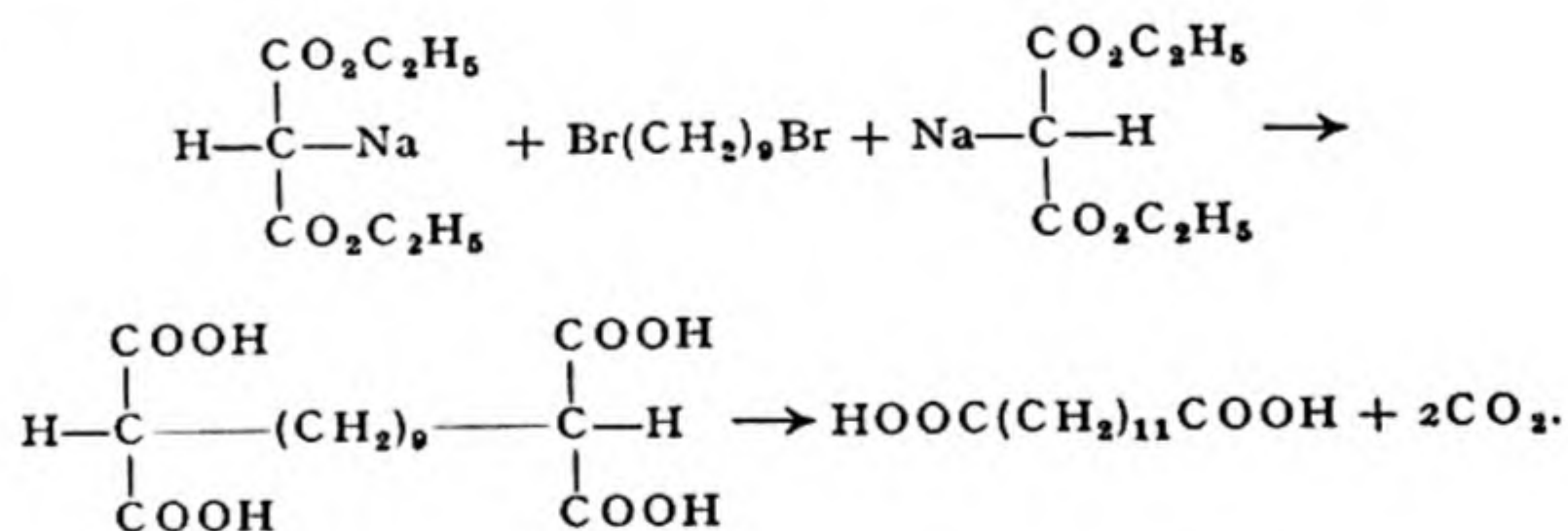
above, can react with a gram atom of sodium. The sodium compound obtained in this way can again react with an alkyl iodide:



By hydrolysing the ester and heating the dibasic acid, a valeric acid, butane 2-carboxylic acid (72) is produced:

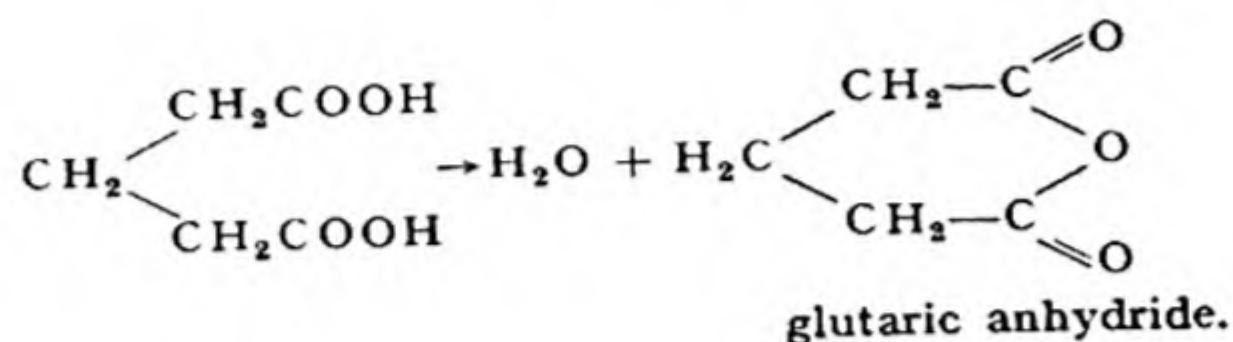
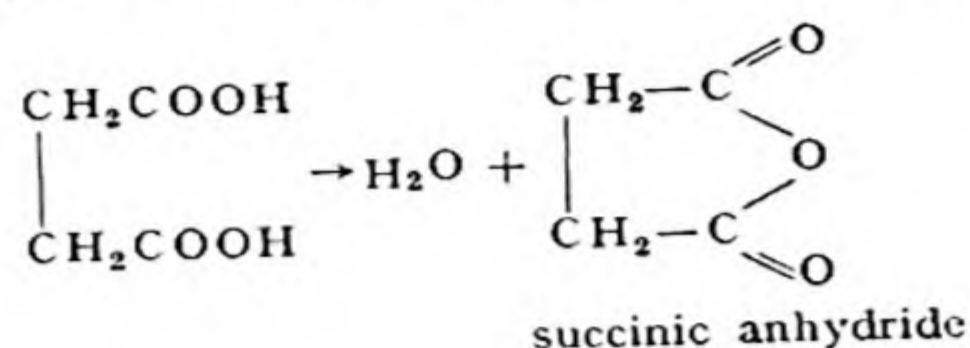


The malonic ester synthesis is also used for the synthesis of the higher members of this series. For example, one may start from heptane dicarboxylic acid, $\text{COOH}(\text{CH}_2)_7\text{COOH}$ ($\text{C}_9\text{H}_{16}\text{O}_4$). The ester of this acid is reduced with sodium in boiling alcohol by the method of BOUVEAULT and BLANC (77) to nonane-1,9-diol, from which 1,9-dibromononane is prepared by the action of hydrobromic acid. By the action of two molecules of sodium ethyl malonate on the dibromo-compound and subsequent hydrolysis, a tetracarboxylic acid is obtained, which gives *undecane 1,11-dicarboxylic acid*, $\text{C}_{13}\text{H}_{24}\text{O}_4$, on heating:



Nonane 1,9-dicarboxylic acid, $\text{COOH}(\text{CH}_2)_9\text{COOH}$, can be produced by allowing potassium cyanide to interact with dibromononane and hydrolysis of the dinitrile so obtained.

124. Ethane 1,2-dicarboxylic acid; succinic acid $\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$. Succinic acid occurs in amber, fossil wood and in many plants, including vines and sugar-beet. The structure of succinic acid follows from the following syntheses:



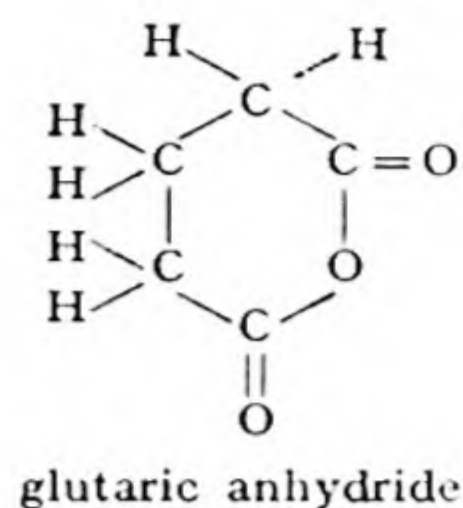
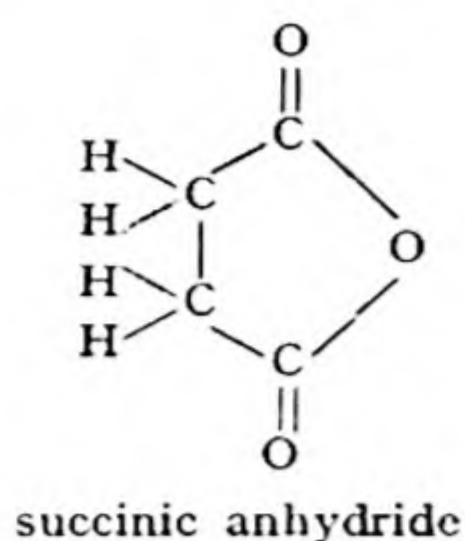
These anhydrides are fairly readily converted into the corresponding dibasic acids by warming with water. The anhydrides of succinic acid and glutaric acid contain a ring consisting of one oxygen atom and four and five carbon atoms, respectively. When ammonium succinate is heated rapidly,

succinimide $\begin{array}{c} \text{CH}_2\text{C}=\text{O} \\ | \quad \quad \diagdown \\ \quad \quad \quad \text{NH} \\ | \quad \quad \diagup \\ \text{CH}_2\text{C}=\text{O} \end{array}$ is produced containing a ring consisting of four carbon atoms and one nitrogen atom.

As with the anhydrides of alkane diols (110) and with cyclic imines (342), rings of five and six atoms are easily formed in this case also. These facts are in agreement with our knowledge of the spatial structure of these molecules. In 37 it is shown that the carbon atoms in the grouping $-(\text{CH}_2)_n-$ form a zigzag chain, in which the angles between the carbon bonds are about 109° . The angle between the oxygen-carbon bonds in an ether is about 110° (79). The molecule of succinic anhydride contains a five-ring formed of four carbon atoms and one oxygen atom. This ring can be formed without the valency bonds undergoing any significant deflection, since the angle in a regular pentagon is equal to 108° . It is to be expected therefore that succinic anhydride will be easily formed.

The same reasoning holds for the formation of glutaric anhydride the molecule of which contains a ring of five carbon atoms and one oxygen atom; in the formation of this six-ring the deflection of the directions of the valency bonds is not large (the angle in a regular hexagon is 120°).

In the formation of the anhydride from malonic acid a four-ring must be formed, which must bring about a very great deflection in the directions of the valency bonds. Hence the anhydride of malonic acid is unknown. The same considerations hold for the anhydrides of the alkane diols. The above explanation was given in a qualitative sense in 1885 by BAEYER in his strain theory.

(b) *Dibasic unsaturated acids**Determination of the configuration of cis- and trans-isomers*

126. The simplest compounds in this group are the *ethene 1,2-dicarboxylic acids* $C_4H_4O_4$. Two compounds having this composition are known, *fumaric acid* and *allofumaric* or *maleic acid*. Fumaric acid occurs in the vegetable kingdom, *e.g.* in toadstools and in common fumitory, *fumaria officinalis*; it sublimes on heating and melts under pressure at 286° ; it is sparingly soluble in water. Maleic acid is not met with in nature; it melts at 130° and is very readily soluble in water.

Both acids can be obtained by heating *malic acid*, *ethanol 1,2-dicarboxylic acid*, $HOOCCH_2CHOHCOOH$; on slow heating to $140-150^\circ$ fumaric acid is the main product, but on rapid heating to 220° the anhydride of maleic acid distils; some fumaric acid is also formed.

Both fumaric acid and maleic acid can be reduced either catalytically or by means of sodium amalgam and water, to succinic acid. Both acids produce malic acid on heating with water and bromosuccinic acid is produced by the addition of hydrobromic acid. Thus the structure of both fumaric acid and maleic acid is represented by the formula $HOOCCH=CHCOOH$.

These acids are stereoisomers of the *cis*- and *trans*-type (compare **82**). In this case it is possible to determine the *stereochemical configuration*, *i.e.* to establish to which of these isomers the *cis*-configuration and to which the *trans*-configuration must be ascribed.

On heating maleic acid to about 160° , water is split off and the internal anhydride, *maleic anhydride*, $C_4H_2O_3$, is produced.

Fumaric acid sublimes at about 200° and is not converted into the anhydride by this treatment; the anhydride of fumaric acid is unknown. Therefore the *cis*-configuration is ascribed to maleic acid (Fig. 30A; projection formula Fig. 30B); in this configuration the carboxyl groups are so situated that water may be split off readily with the formation of a five-membered ring. The *trans*-configuration (Fig. 31A; projection formula Fig. 31B) is ascribed to fumaric acid; in this case the carboxyl groups are so situated that the formation of a ring-structure by the removal of water is not possible,

200 COMPOUNDS WITH TWO OR MORE FUNCTIONAL GROUPS CH. 8
 because this would necessitate a considerable deviation in the bonding angles.

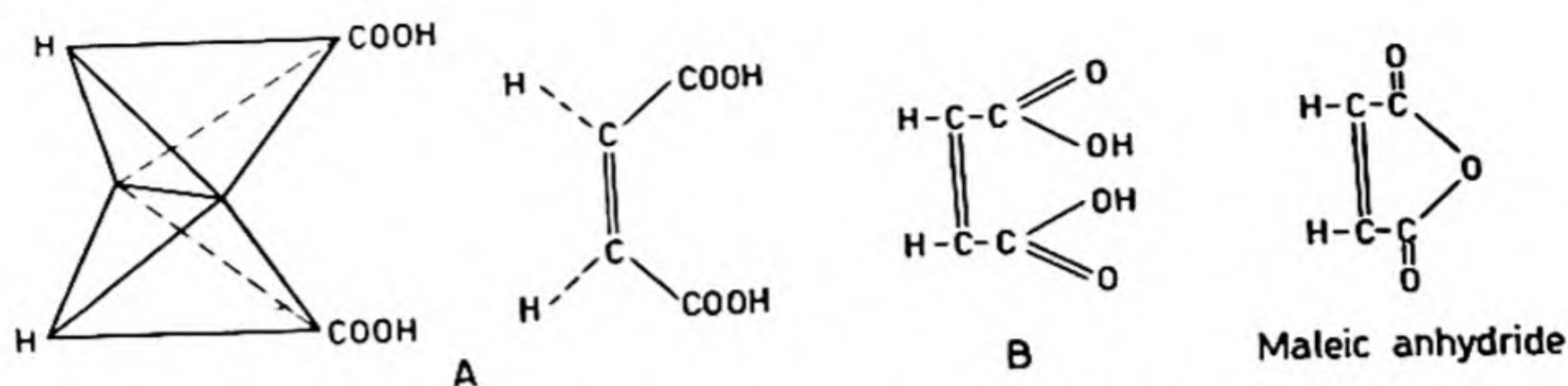


Fig. 30. Maleic acid (*cis*-configuration)

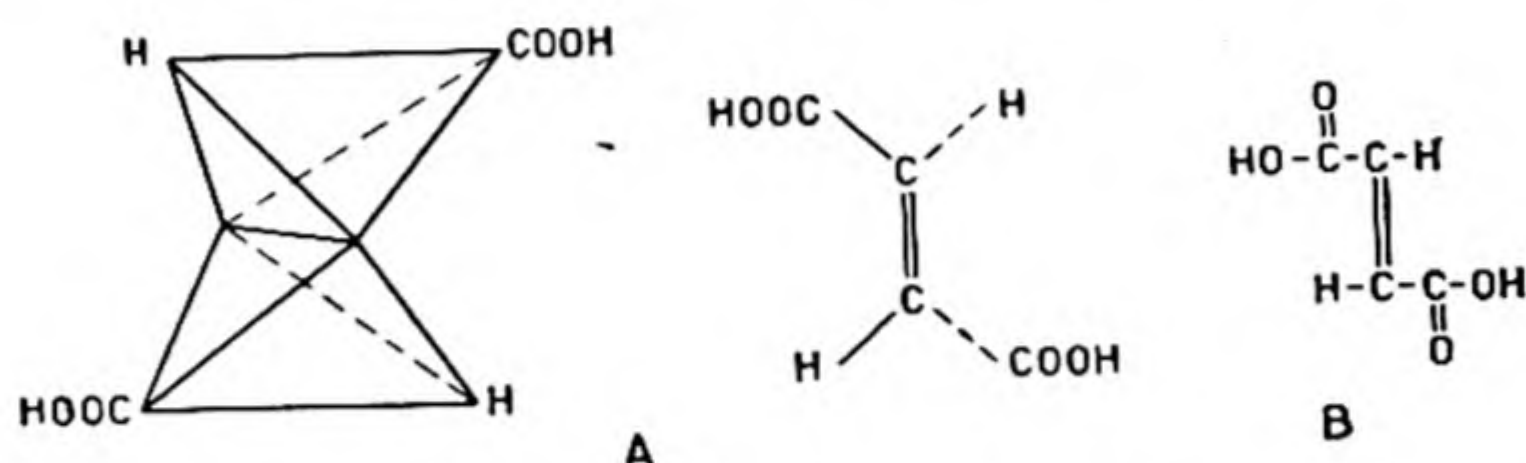
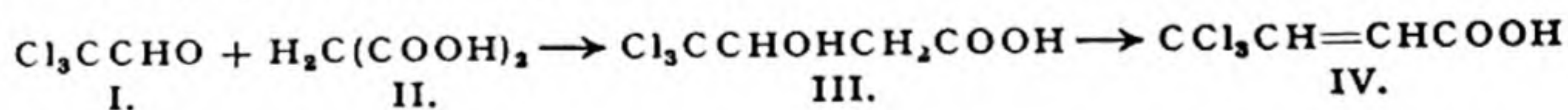


Fig. 31. Fumaric acid (*trans*-configuration)

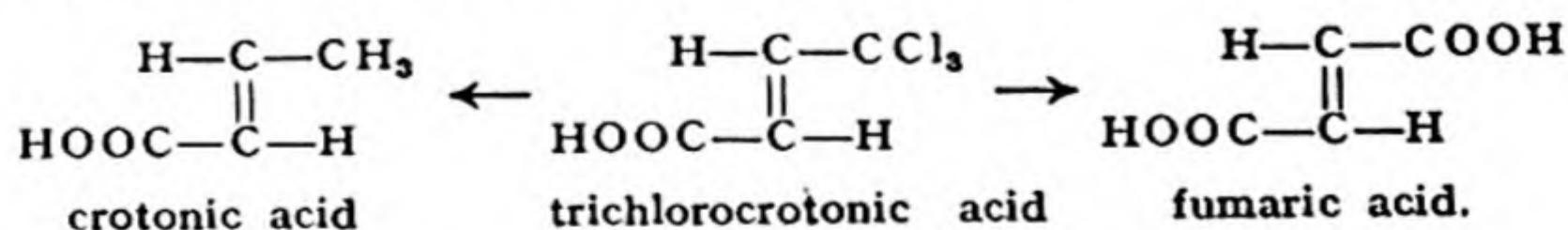
By means of these stereochemical formulae for fumaric and maleic acids it is also possible to explain the conversion of these acids into the stereoisomeric tartaric acids.

Examples of *cis-trans* isomerism in unsaturated mono-carboxylic acids have already been mentioned in 100. There is no generally applicable method for determining the configuration of *cis-trans* isomers, so that in a number of cases it is not known with any degree of certainty to which isomer the *cis*- or *trans*-configuration must be ascribed.

It has been established in the following way that the crotonic acid melting at 71° (100) has a *trans*-configuration (VON AUWERS and WISSEBACH). By warming chloral (I) with malonic acid (II) a trichlorohydroxybutyric acid (III) is prepared from which trichlorocrotonic acid (IV) is obtained by warming with acetic anhydride and sodium acetate:

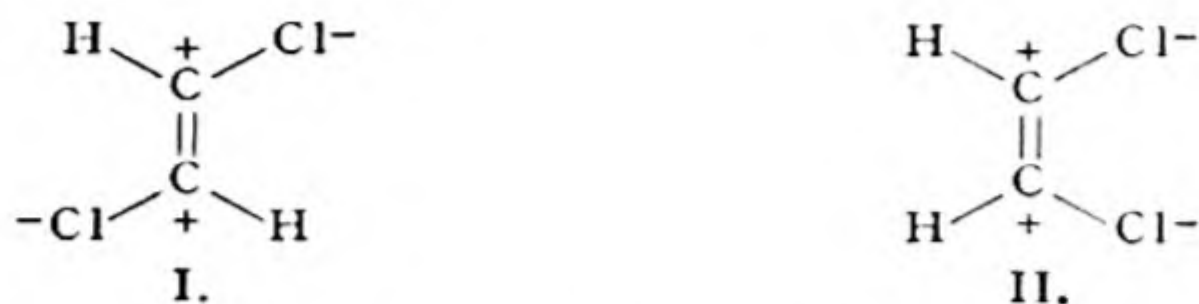


Crotonic acid is obtained from trichlorocrotonic acid by reduction with zinc and acetic acid; on the other hand fumaric acid is formed by hydrolysis with aqueous sulphuric acid; no maleic acid is formed in this case:



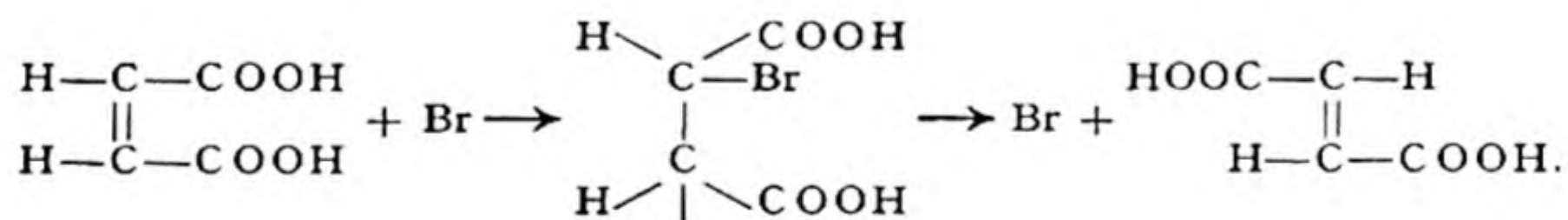
An interesting method of determining configuration is employed in dichloroethene;

this compound occurs in two isomeric forms boiling respectively at 48° and 59° . The former has a dipole moment equal to zero; hence this isomer possesses the *trans*-configuration (I), in which the centres of the positive and negative charges coincide. The isomer boiling at 59° has a dipole moment of 1.89×10^{-18} and therefore possesses the *cis*-configuration (II) (ERRERA).



The distance between the two chlorine atoms in I must then be greater than in II. From measurements on X-ray diffraction by the molecules of these two substances, DEBIJE has calculated that the Cl—Cl distance in the *trans*-isomer is 4.1 \AA and 3.6 \AA in the *cis*-isomer.

Maleic acid can be converted into fumaric acid in various ways, *e.g.* by warming to a temperature just above its melting point. The lack of free rotation in doubly bound carbon atoms is not to be so construed that the conversion of a *cis*- into a *trans*-configuration is impossible under all circumstances. Such transformations may take place with the transfer of energy either by warming or by irradiation when catalytic influences frequently play a rôle. The conversion of oleic acid into elaidic acid has already been discussed in 101. Fumaric acid is produced when a concentrated aqueous solution of maleic acid containing a little bromine is exposed to sunlight. This may be explained as follows: a bromine atom produced by the dissociation of a molecule of bromine, adds on to the double bond between the carbon atoms in maleic acid; in this way there is produced a radical with a free valency bond. When this radical loses its bromine atom again, the double bond between the two carbon atoms is restored in such a way that the more stable configuration, *i.e.* fumaric acid, is produced:

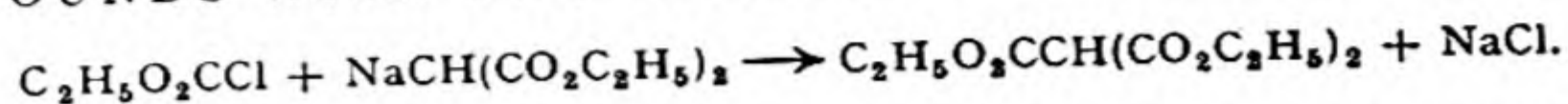


The molecular heat of combustion amounts to 327.5 kcal for maleic acid and to 320.1 kcal for fumaric acid. From this it follows that fumaric acid is the stable modification at ordinary temperatures. Fumaric acid and maleic acid are mutually interconvertible by irradiation with ultra-violet light.

As with the monobasic unsaturated acids, the *affinity* constant in the dibasic unsaturated acids is greater than in the corresponding saturated acids; *k* for succinic acid is 0.0000665 and 0.00093 for fumaric acid. For maleic acid *k* is 0.0117 , *i.e.* almost twelve times greater than for fumaric acid. Hence the distance of the carboxyl groups in the molecule of these acids has an effect on the strength of the acids.

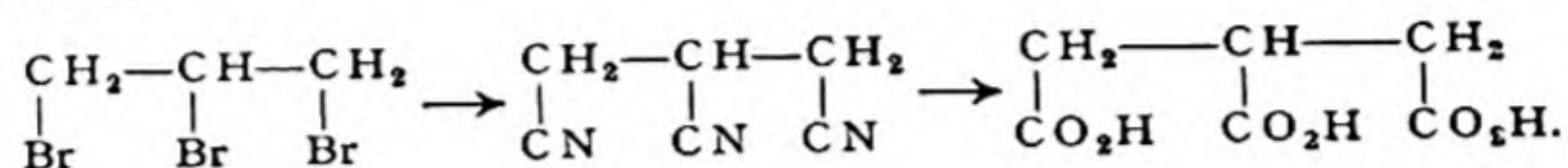
(c) Tribasic acids

127. Esters of acids with three or four carboxyl groups on one carbon atom are known but the acids themselves are not. The triethyl ester of *methane tricarboxylic acid*, for example, is obtained by the action of ethyl chloroformate (150) on sodium ethyl malonate (123):

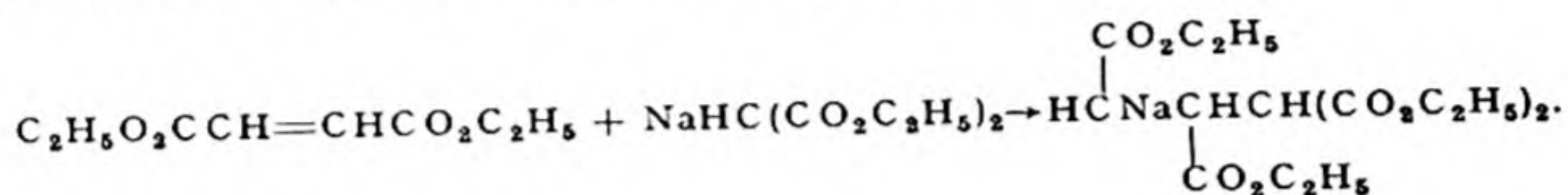


By the repeated action of ethyl chloroformate on the sodium compound of tri-ethylmethane tricarboxylate, tetraethylmethane tetracarboxylate is produced. By hydrolysing these esters with sulphuric acid, carbon dioxide is split off; malonic acid is produced instead of the expected tri- or tetra-basic acid.

Propane 1,2,3-tricarboxylic acid, tricarballic acid (m.p. 165°) is an example of an acid with three carboxyl groups on different carbon atoms. This acid can be obtained by treating tribromopropane with potassium cyanide and hydrolysing the tricyanopropane which is formed:



Another synthesis of polybasic acids depends on the addition of sodium ethyl malonate to esters of unsaturated acids, e.g. to diethyl fumarate



Propane 1,2,3-tricarboxylic acid is obtained by hydrolysis followed by splitting off of carbon dioxide.

Propene 1,2,3-tricarboxylic acid (m.p. 191°), also called *aconitic acid*, because of its occurrence in *aconitum napellus*, is an example of an unsaturated tricarboxylic acid. It is obtained by heating citric acid (144) when water is split off. The structure of propene tricarboxylic acid is $\begin{array}{c} \text{CH}=\text{C}-\text{CH}_2 \\ | \quad | \quad | \\ \text{CO}_2\text{H} \quad \text{CO}_2\text{H} \quad \text{CO}_2\text{H} \end{array}$, for on reduction it is converted

into propane 1,2,3-tricarboxylic acid.

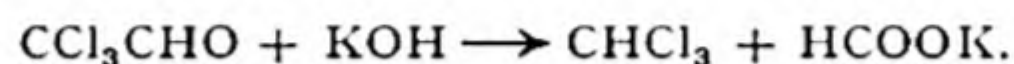
(vi) HALOGENO-DERIVATIVES OF ALDEHYDES

128. *Trichloroethanal* or *chloral*, CCl_3CHO , belongs to this group of compounds. This substance, which is of importance in several ways, is prepared by the action of dry chlorine gas on absolute alcohol (LIEBIG). In this process several reactions take place one after the other; first of all *ethyl hypochlorite* is produced: $\text{CH}_3\text{CH}_2\text{OH} + \text{Cl}_2 \rightarrow \text{CH}_3\text{CH}_2\text{OCl} + \text{HCl}$. This substance decomposes into hydrogen chloride and ethanal: $\text{CH}_3\text{CH}_2\text{OCl} \rightarrow \text{CH}_3\text{CHO} + \text{HCl}$. The ethanal is then chlorinated via various intermediate products to trichloroethanal: the end-product from this reaction is a compound of trichloroethanal with ethanol $\text{CCl}_3\text{CH} \begin{array}{l} \nearrow \text{OC}_2\text{H}_5 \\ \searrow \text{OH} \end{array}$. Trichloroacetaldehyde is

obtained from this compound by treatment with concentrated sulphuric acid. It is a viscous liquid with a characteristic odour. It melts at -57° and boils at 98° . When this substance is brought into contact with water, a crystalline substance, *chloral hydrate*, $\text{CCl}_3\text{CHO} \cdot \text{H}_2\text{O}$ (m.p. 47°) is produced

with the evolution of heat. Because the hydrate is stable it is represented by the formula $\text{CCl}_3\text{CH}(\text{OH})_2$. Hence this is a compound in which two hydroxyl groups are attached to the same carbon atom.

A solution of chloral hydrate does *not* show all the reactions of aldehydes, *e.g.* no colour is produced with fuchsin-sulphur dioxide. But it reduces ammoniacal silver solution and is oxidised to trichloroacetic acid by nitric acid. Chloral is broken up by alkaline liquids into chloroform and an alkali formate even at room temperatures:



This reaction takes place with measurable velocity in very dilute solutions and is monomolecular. This can be explained by postulating that the initial product is an addition compound consisting of one molecule of chloral and one molecule of the

base, $\text{CCl}_3\text{CH} \begin{smallmatrix} \nearrow \text{OH} \\ \searrow \text{OK} \end{smallmatrix}$, which then decomposes with measurable velocity into chloroform and alkali formate. The electrical conductivity of a solution of chloral hydrate and potassium hydroxide also points to a combination of these two molecules (ENKLAAR).

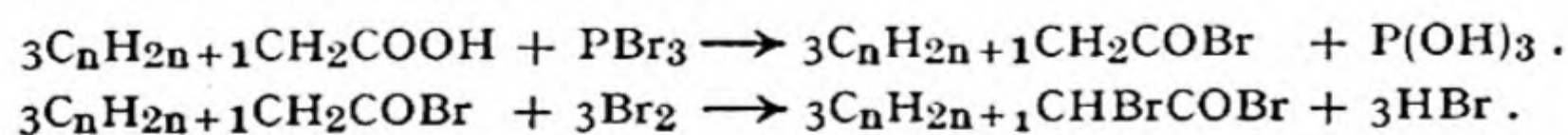
In 1869 LIEBRICH discovered that chloral hydrate can be used as a hypnotic; in this connection he set out from the idea that chloral should be split up in the organism with the formation of chloroform. Later on it appeared, however, that chloral is reduced in the body to trichloroethanol, which is eventually eliminated by the body in the form of a complex compound (urochloralic acid). Since improved soporifics have appeared on the market the use of chloral medicinally is now obsolete.

(vii) SUBSTITUTED ACIDS

(a) *Acids with halogen atoms in the alkyl-groups*

129. These acids are produced by the action of chlorine or bromine on anhydrous alkane carboxylic acids in the presence of a substance such as sulphur, iodine or red phosphorus, which acts as a "halogen carrier". Thus *monochloroacetic acid* can be prepared by treating glacial acetic acid containing a little red phosphorus with chlorine at 100° . The reaction is greatly accelerated by sunlight.

For the preparation of brominated acids an equivalent quantity of red phosphorus is usually employed. The acid bromide is first of all produced, which is more easily brominated in the alkyl group than the alkane carboxylic acid itself (HELL, VOLHARD, ZELINSKY):



On the addition of water, the bromine combined in the $-\text{COBr}$ -group is replaced by OH, so that the acid $\text{C}_n\text{H}_{2n+1}\text{CHBrCOOH}$ is produced. It has been found that bromination by this method succeeds only with acids in

which the carbon atom attached to the carboxyl group carries at least one atom of hydrogen, so that α - or 1-halogeno-acids are produced. Trimethylacetic acid $(\text{CH}_3)_3\text{CCOOH}$ and tetramethylsuccinic acid $\text{HOOC}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{COOH}$ cannot be brominated in this way.

Halogenated acids can be obtained also by the addition of hydrogen halides to unsaturated acids or by the action of phosphorus halides on hydroxy-acids (130). The iodinated acids are produced by warming the chlorinated or brominated acids with potassium iodide.

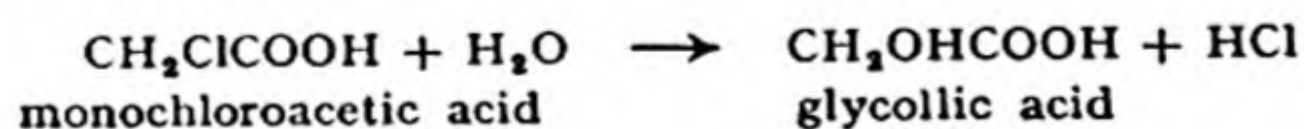
The dissociation constants of the halogenated acids are considerably greater than those of the corresponding alkane carboxylic acids (see Table 33). The effect of the fluorine atom is greatest and that of the iodine atom least. The increase in the dissociation constant is smaller the further removed the halogen atom is from the carboxyl group.

TABLE 33
DISSOCIATION CONSTANTS OF SOME HALOGENATED ACETIC AND BUTYRIC ACIDS

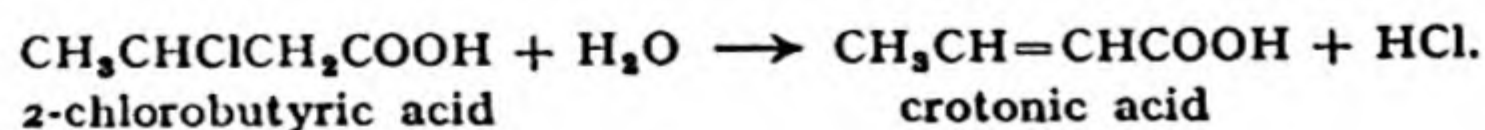
Name	Formula	k at 25°
Acetic acid	CH_3COOH	0.0000184
Fluoroacetic acid	CH_2FCOOH	0.00218
Chloroacetic acid	CH_2ClCOOH	0.00155
Bromoacetic acid	CH_2BrCOOH	0.00138
Iodoacetic acid	CH_2ICOOH	0.00076
Dichloroacetic acid	CHCl_2COOH	0.0514
Trichloroacetic acid	CCl_3COOH	0.300
Butyric acid	$\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$	0.0000175
1-Chlorobutyric acid	$\text{CH}_3\text{CH}_2\text{CHClCOOH}$	0.00139
2-Chlorobutyric acid	$\text{CH}_3\text{CHClCH}_2\text{COOH}$	0.000089
3-Chlorobutyric acid	$\text{CH}_2\text{ClCH}_2\text{CH}_2\text{COOH}$	0.000030 (approx.)

The halogen atom in the halogeno-acids can be replaced by various groups of atoms such as $-\text{NH}_2$, $-\text{OH}$, $-\text{CN}$, etc., just like the halogen atoms in halogenoalkanes. Therefore, the halogeno-acids are of great importance in a number of syntheses.

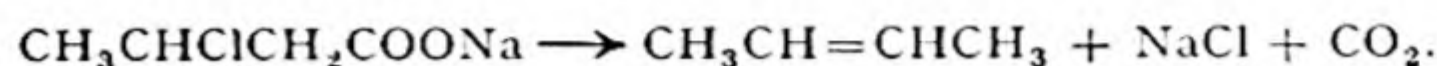
While 1-halogeno-acids are converted into hydroxy-acids (131) by boiling with excess water or with dilute alkalis,



under the same conditions hydrogen halide is split off from 2-halogeno-acids with the formation of unsaturated acids (99):



It is noteworthy that on warming 2-chloro-acids with a solution of soda, decomposition goes further; carbon dioxide is eliminated and an alkene is produced:

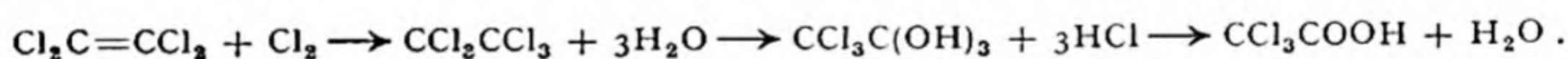


Monochloroacetic acid (m.p. 63° , b.p. 189°) is used, for example, in the synthesis of indigo (**316**); *dichloroacetic acid* is a liquid boiling at 195° .

Trichloroacetic acid (m.p. 57° , b.p. 195°) can be prepared by the oxidation of chloral (**128**). It is split up into carbon dioxide and chloroform on warming with water to 100° , $\text{CCl}_3\text{COOH} \rightarrow \text{CO}_2 + \text{CHCl}_3$, a fact which must be ascribed to the plurality of negative groups in the molecule. A similar case is to be found in the decomposition of chloral by dilute alkalis discussed in the preceding section.

Trichloroacetic acid was obtained by DUMAS in 1839 by the long continued action of chlorine on acetic acid. DUMAS established that in this compound, in which all the hydrogen atoms in the alkyl group had been replaced by chlorine, the characteristic properties of a carboxylic acid were still maintained. This investigation was of great importance for the theory of substitution reactions.

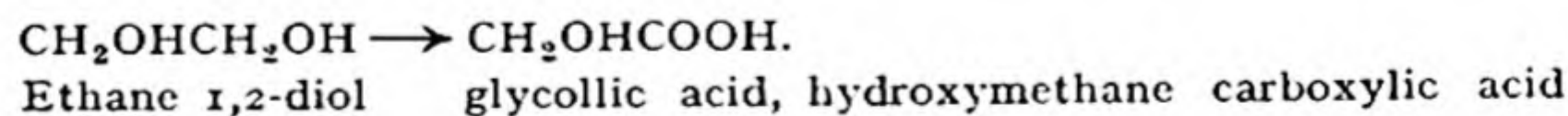
In 1845 KOLBE obtained acetic acid by treating trichloroacetic acid with sodium amalgam and water. In this way the synthesis of acetic acid from its elements was realised as KOLBE had prepared trichloroacetic acid in the following way: Carbon disulphide (obtained by the action of sulphur on carbon at a high temperature) was converted into carbon tetrachloride by treatment with chlorine, from which tetrachloroethene $\text{Cl}_2\text{C}=\text{CCl}_2$ was prepared by heating. The tetrachloroethene was treated in sunlight with water and chlorine and trichloroacetic acid was produced.



(b) *Monobasic hydroxy-acids*

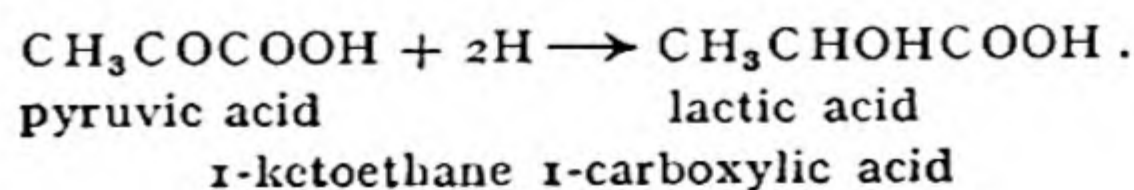
130. These hydroxy-acids are compounds containing a carboxyl group and one or more hydroxyl groups. When only one hydroxyl group is present they are called monohydroxy-acids; they may be prepared by the following methods.

1. By the careful oxidation of polyhydric alcohols, *e.g.* by warming with nitric acid:

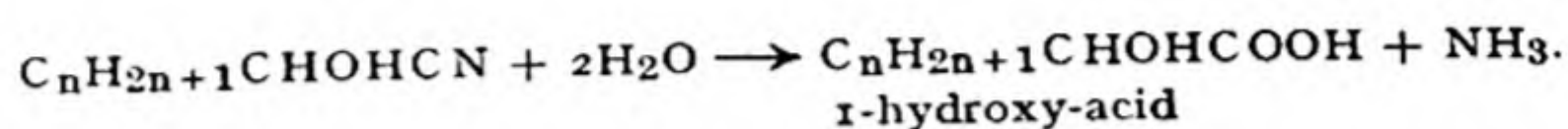
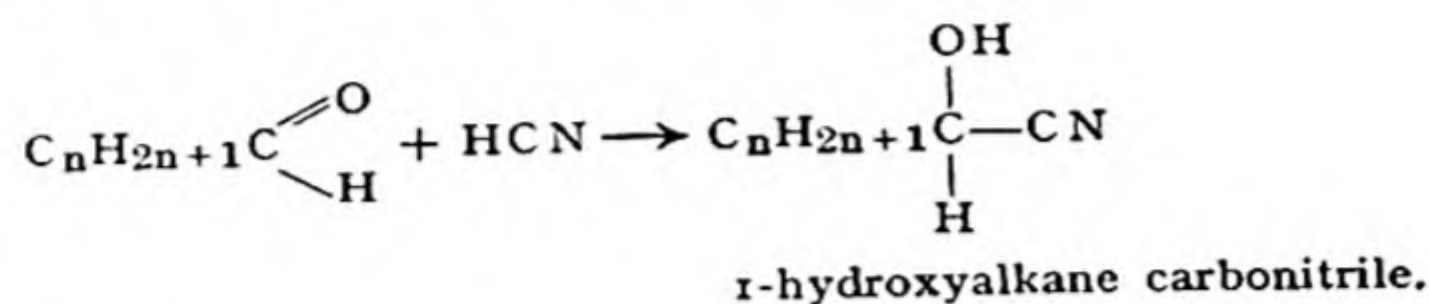


2. By replacing the halogen atom in 1-halogeno-acids (**129**) by the hydroxyl group, *e.g.* by boiling with dilute alkalis.

3. By the reduction of acids which contain a carbonyl group as well as a carboxyl group (aldehydo- or keto-acids, see **147**):



4. By addition of hydrogen cyanide to aldehydes or ketones and hydrolytic fission of the hydroxycarbonitrile so obtained. In this way α -hydroxy-acids (α -hydroxy-acids) are formed exclusively:



The acids, which are brominated by the VOLHARD method (see 129), give hydroxy-acids when the bromine is replaced by hydroxyl. These hydroxy-acids are produced also by the *cyanhydrin synthesis* just described. From this it follows that the bromine atom in the brominated acids is attached to the carbon atom carrying the carboxyl group.

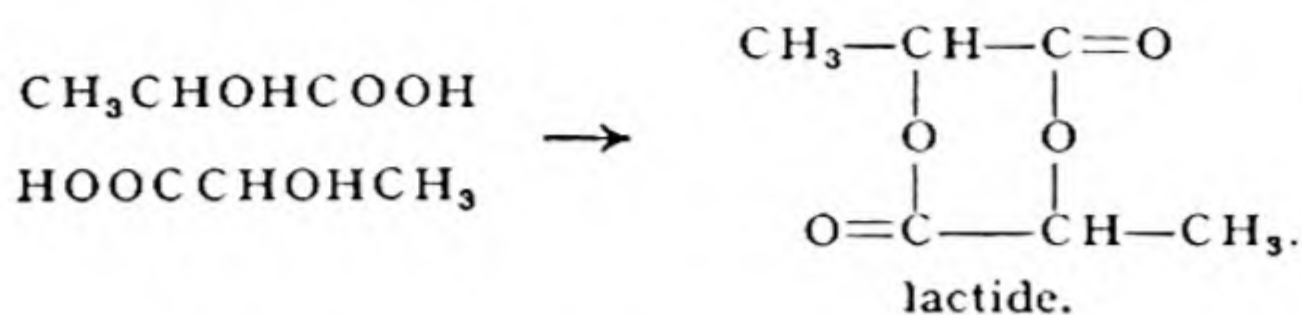
Properties. The dissociation constant of the hydroxy-acid is greater than that of the alkane carboxylic acid with the same number of carbon atoms (see Table 34). The effect on the dissociation constant is greatest when the hydroxyl group is situated next to the carboxyl group.

TABLE 34
DISSOCIATION CONSTANTS OF SOME HYDROXY-ACIDS

Name	Formula	k
Acetic acid	CH_3COOH	0.0000186
Glycollic acid (hydroxyacetic acid)	CH_2OHCOOH	0.000152
Propionic acid	$\text{CH}_3\text{CH}_2\text{COOH}$	0.0000138
Lactic acid (1-hydroxypropionic acid)	$\text{CH}_3\text{CHOHCOOH}$	0.000138
2-Hydroxypropionic acid	$\text{CH}_2\text{OHCH}_2\text{COOH}$	0.000031

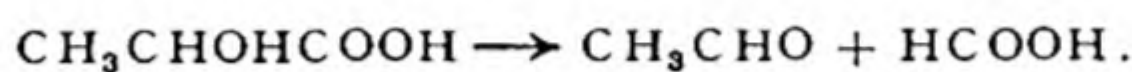
Both the hydrogen atom in the carboxyl group and that in the hydroxyl group can be replaced by an alkyl residue. In the former case an ester is produced, *e.g.* ethyl glycollate $\text{CH}_2\text{OHCOOC}_2\text{H}_5$, which can be hydrolysed, while in the latter case an acid ether, *e.g.* ethoxyacetic acid $\text{C}_2\text{H}_5\text{OCH}_2\text{COOH}$, is formed, from which the alkyl group *cannot* be removed by hydrolysis.

The *α -hydroxy-acids* (α -hydroxy-acids) can easily split off water, two molecules of hydroxy-acid reacting in such a way that the OH-group in one molecule reacts with the COOH-group in the second molecule with the formation of *lactides*. *Lactide*, m.p. 125° , is produced from lactic acid by heating under diminished pressure:



Thus this compound contains two ester groupings. It may therefore be split up hydrolytically by warming with water or with dilute acids, with the formation of lactic acid.

Many 1-hydroxy-acids are split up into formic acid and an aldehyde by warming with dilute sulphuric acid, *e.g.*

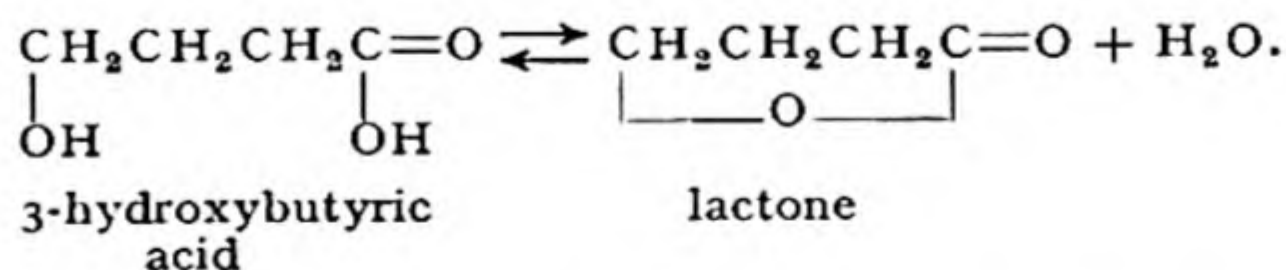


2-Hydroxy-acids (β -hydroxy-acids) also split off water on heating but with the production of unsaturated acids. The same reaction occurs on warming an aqueous solution of the sodium salt of a 2-hydroxy-acid with dilute caustic soda. A state of equilibrium is set up in this reaction (FITTIG). From 2-hydroxybutyric acid there is produced crotonic acid along with a small amount of vinylacetic acid:



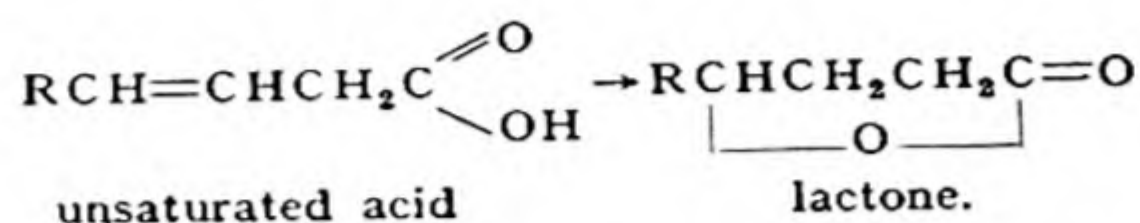
On evaporating their solutions *3-hydroxy-acids* (γ -hydroxy-acids) split off water and are converted into γ -lactones, which may be regarded as internal esters. Because 3-hydroxy-acids are rather unstable in the free state, as a rule they are not known in a state of purity, but the salts, esters or amides are known.

On warming with water the lactones are gradually converted into the corresponding hydroxy-acids. The reaction is reversible and leads to a state of equilibrium, which lies at about 80 % of lactone for butyrolactone at 100° in a 1 % aqueous solution:



This is a new example of the fact that cyclic compounds with five atoms in the ring are easily produced (see 125). The lactones may add on hydrobromic acid and ammonia as well as water. By addition of HBr, 3-bromoacids are produced, from which lactones can be regenerated. By addition of NH_3 , amides of 3-hydroxy-acids are produced. As far as the lower members are concerned, lactones are colourless liquids, which may be distilled

without decomposition. These compounds are easily converted into the alkali salts of 3-hydroxy-acids by alkali hydroxides but they are not affected by sodium carbonate in aqueous solution. Lactones may also be produced by warming acids with a double bond in the 2- or 3-positions, with dilute sulphuric acid:



δ-Lactones may be formed from 4- and 5-hydroxy-acids, and in general they are reconverted into hydroxy-acids more easily than the γ-lactones.

It is noteworthy, that in the vegetable kingdom, lactones occur in which the ring system consists of a large number of carbon atoms. A lactone occurs in angelica root (*Archangelica officinalis*), having the structure $\text{CH}_2(\text{CH}_2)_{13}\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{O} \end{array}$, and possessing an odour of musk. This compound can be prepared by the action of moist silver oxide on 14-bromotetradecane-1-carboxylic acid, $\text{BrCH}_2(\text{CH}_2)_{12}\text{CH}_2\text{COOH}$.

131. Some individual hydroxy-acids will now be considered in more detail.

Hydroxymethane carboxylic acid, glycollic acid (m.p. 80°) CH_2OHCOOH , occurs in unripe grapes and can be prepared from monochloroacetic acid by boiling with water and calcium carbonate.

1-Hydroxyethane 1-carboxylic acid, 1-hydroxypropionic acid or lactic acid $\text{CH}_3\text{CHOHCOOH}$. The structure of this acid follows from its synthesis from hydrocyanic and acetaldehyde (see 58); in this way a mixture of equal quantities of dextro-rotatory and laevo-rotatory lactic acid is produced.

Lactic acid is produced by the action of certain bacteria on particular kinds of sugars such as grape-sugar, cane-sugar, malt-sugar and milk-sugar. This decomposition is known as lactic acid fermentation. It depends on the species of bacteria whether laevo-rotatory lactic acid or a mixture of dextro- and laevo-rotatory lactic acid is produced. *l*-Lactic acid occurs in sour milk as was observed as long ago as 1780 by SCHEELE; it is produced by the decomposition of milk-sugar by *bacillus lactis acidii*.

Anhydrous *dl*-lactic acid melts at 18° and is very readily soluble in water; *d*- and *l*-lactic acids melt at 26°.

Lactic acid is prepared on a technical scale by the action of suitable bacteria (*e.g.* *B. DELBRÜCKI* or *B. lactis acidii* LEICHMANN) on glucose or cane-sugar. Since development of the bacteria is retarded by the acid as it is formed, calcium carbonate is added to remove the free acid and calcium lactate results. Lactic acid also occurs in pickle-cabbage and in "press fodder" (compressed grass or clover). It is also a constituent of gastric juice. It can be prepared from glucose also by the action of caustic soda solution but other decomposition products are produced simultaneously.

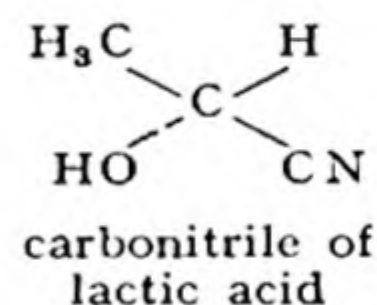
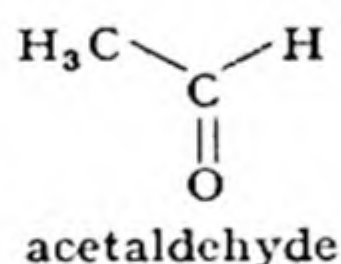
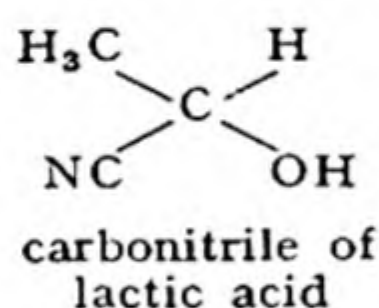
Lactic acid is used in leather tanneries for making skins supple, in textile industries and for making lemonade. Calcium lactate is used in medicine; sodium and potassium lactates are extremely soluble in water.

Dextro-rotatory lactic acid or *sarcosolactic acid* occurs in muscle in which it is formed from glycogen (184).

2-Hydroxypropionic acid $\text{CH}_2\text{OHCH}_2\text{COOH}$ can be obtained from 2-bromopropionic acid by treatment with silver oxide and water. On heating it is converted into acrylic acid $\text{CH}_2=\text{CHCOOH}$.

2-Hydroxybutyric acid (β -hydroxybutyric acid) $\text{CH}_3\text{CHOHCH}_2\text{COOH}$, can be prepared for example by oxidising aldol $\text{CH}_3\text{CHOHCH}_2\text{CHO}$. The laevo-rotatory form of 2-hydroxybutyric acid occurs in urine in certain pathological conditions (*diabetes mellitus*).

132. It has already been mentioned, that in the synthesis of an α -hydroxy-acid from an aldehyde and hydrogen cyanide, a mixture of equal amounts of the *d*- and the *l*-isomer is produced. The cause of this is apparent from a consideration of stereochemical models, in which the $\text{C}=\text{O}$ bond lies in the plane of the drawing, and the $\text{C}-\text{CH}_3$ bond and the $\text{C}-\text{H}$ bond lie respectively in front of and behind this plane:



Addition of HCN can occur in two ways according to whether one or other of the bonding forces of the $\text{C}=\text{O}$ bond is broken and becomes available for attachment of the CN -group. In this way two mirror image configurations are produced, which cannot be superimposed and which represent the *d*- and the *l*-forms of 1-hydroxyethane carbonitrile. Since the $\text{C}=\text{O}$ bond in acetaldehyde is symmetrically situated with respect to the plane of the $\text{C}-\text{CH}_3$ bond and the $\text{C}-\text{H}$ bond, the chance for either mode of addition is equally great, so that equal quantities of the *d*- and the *l*-forms will be produced.

An example in which an asymmetrical carbon atom is obtained by substitution, is the formation of 1-bromopropionic acid $\begin{array}{c} \text{Br} \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{COOH} \end{array}$ from propionic acid $\begin{array}{c} \text{H} \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{COOH} \end{array}$. According to whether one or other of the

H-atoms is substituted, opposite rotatory acids will be produced and here also the chance of the formation of one or the other is equally great, since the two H-atoms available for substitution are situated symmetrically with

regard to the plane containing the C—CH₃ and the C—COOH bonds.

A third possibility for the occurrence of an asymmetric carbon atom exists in the splitting of a group. An example is the formation of butane

2-carboxylic acid $\begin{array}{c} \text{H}_3\text{C} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{CH}_3\text{H}_2\text{C} \quad \text{COOH} \end{array}$ from butane 2,2-dicarboxylic acid $\begin{array}{c} \text{H}_3\text{C} \quad \text{COOH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{H}_3\text{C} \quad \text{COOH} \end{array}$ by splitting off a molecule of carbon dioxide. Since either one or other of the two carboxyl groups can be broken off in this reaction with equal facility, a mixture of equal quantities of *d*- and *l*-forms is produced in this case also.

In general, in the synthesis of compounds with an asymmetric carbon atom, an inactive mixture of a racemic compound of the d- and l-form is obtained, if the synthesis is carried out on compounds containing no asymmetric carbon atoms.

The optically active lactic acids and many other optically active substances are converted at high temperatures into the inactive mixture, which consists of equal parts of laevo- and dextro-rotatory substances. For this to happen half of the active substance must be converted into its optical isomeride. The velocity with which this reaction occurs can vary over a very wide range. While long continued heating is necessary with some active substances there are others which change over into the inactive (racemic) mixture at ordinary temperatures.

(c) Dibasic hydroxy-acids

133. Methanol dicarboxylic acid, *tartronic acid*, COOHCHOHCOOH, is the first member of this series. It is produced by oxidation of ethane 1,2-diol carboxylic acid (glyceric acid) with nitric acid. At the melting point (187°) carbon dioxide is split off; glycollic acid CH₂OHCOOH which should be produced, loses water and passes over into a polymer of the corresponding lactide (131).

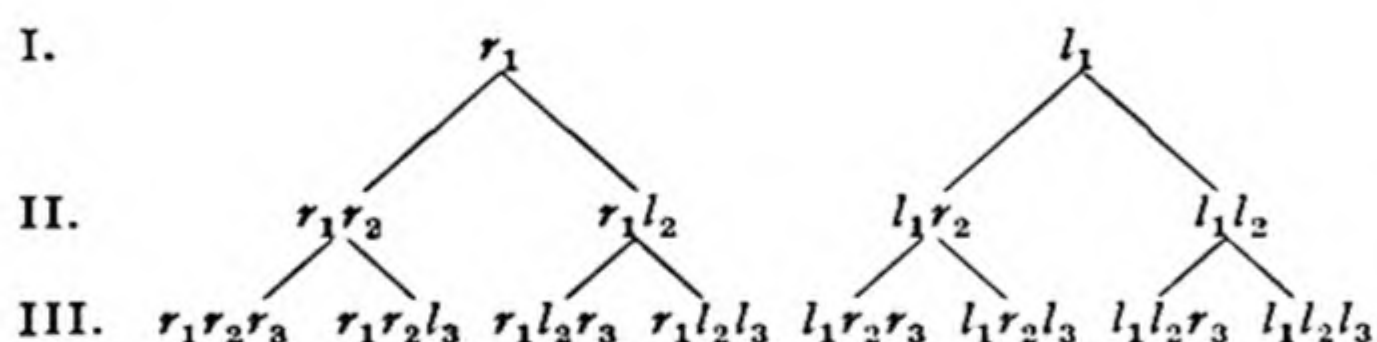
Malic acid, ethanol 1,2-dicarboxylic acid or *1-hydroxysuccinic acid*, COOHCHOHCH₂COOH, occurs in various unripe fruits and can be prepared from unripe rowan berries. It melts at 100° and is readily soluble in water and alcohol. Occurring in the vegetable kingdom it is laevo-rotatory.

The structure of malic acid is determined as follows. Reduction with hydriodic acid produces succinic acid. An ester of monochlorosuccinic acid is produced by the action of phosphorus pentachloride on the ester of malic acid. The presence of an alcoholic hydroxyl group also follows from the fact that an acetate is formed from diethyl malate by treatment with acetyl chloride. The formation of fumaric and maleic acids on heating malic acid, has already been discussed (126). Conversely, fumaric acid can be converted

into malic acid by heating with water; in this case the inactive form is produced.

134. *Ethane 1,2-diol 1,2-dicarboxylic acids* or *tartaric acids* $C_4H_6O_4$. Four stereoisomeric acids of the formula $COOHCHOHCHOHCOOH$ are known, viz. dextro-rotatory and laevo-rotatory tartaric acids, racemic acid and meso-tartaric acid; the last two acids are optically inactive. These inactive forms are produced by the cyanhydrin synthesis from ethane dial (glyoxal 145) or by heating the silver salts of the dibromosuccinic acids (obtained from fumaric or maleic acids and bromine) with water. The structural formula follows from this method of formation.

According to this formula two asymmetric carbon atoms occur in the molecule of the tartaric acids. When there is one asymmetric carbon atom present in a molecule two optically active isomers are possible. When the molecule contains a second asymmetric carbon atom, this may be either dextro- or laevo-rotatory, so that the combinations II in the scheme given below, in which r and l represent dextro- and laevo-rotatory carbon atoms respectively, are possible. When there are three asymmetric carbon atoms it may be shown in the same way, that the number of isomers (combinations III) theoretically possible is $2^3 = 8$, i.e. for n asymmetric carbon atoms the number is 2^n .



In this derivation it is assumed that the various asymmetric carbon atoms are dissimilar, i.e. carry different atoms or groups of atoms and the racemic combinations are not taken into account. In the tartaric acids the two asymmetric carbon atoms are attached to the same groups, i.e. both asymmetric carbon atoms are equivalent.

Consequently, cases $r_1 l_2$ and $l_1 r_2$ become identical so that three isomers are to be expected. Since however 1 and 3 (below) can form a racemic compound, racemic acid, altogether there are four stereoisomers, viz.

CH(OH) (COOH)	1	2	3	4
	dextro	dextro	laevo	inactive combination of 1 + 3.
CH(OH) (COOH)	dextro	laevo	laevo	
	1. dextro-tartaric acid,		3. laevo-tartaric acid,	
	2. meso-tartaric acid,		4. racemic acid.	

Racemic acid is an addition compound of dextro- and laevo-tartaric acids.

It may be resolved into its optical components. On the other hand, meso-tartaric acid consists of one species of molecules, which are inactive. Hence it cannot be resolved into optically active forms, since the molecule is internally compensated.

Projection formulae are used for representing the stereochemical configuration of compounds with more than one asymmetric carbon atom (E. FISCHER).

Fig. 33 is the projection of Fig. 32, the space model of a compound in which two asymmetric carbon atoms occur.

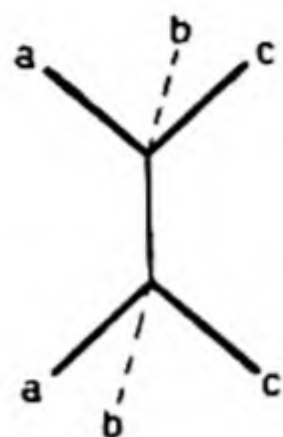


Fig. 32. Space model of a compound with two asymmetric C-atoms

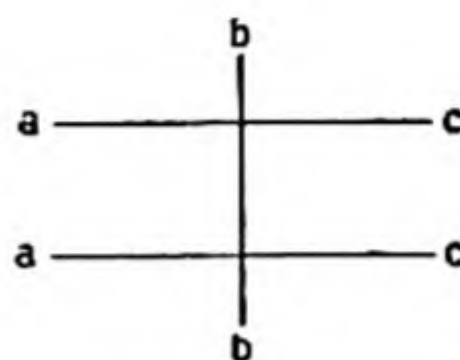


Fig. 33. Projection of Fig. 32

The bonds *a* and *c*, which lie in front of the plane of the paper in Fig. 32, correspond with the line *ac*, which lies at right angles to the line joining the carbon atoms in Fig. 33. The bonds *b* lie behind the plane of the paper in Fig. 32 and are projected in Fig. 33 as extensions of the line joining the carbon atoms.

The order of the atoms or groups of atoms, *a*, *b* and *c*, around the asymmetric carbon atom is not altered when one carbon atom is rotated with respect to the other, see Fig. 34; the configurations of Figs. 32 and 34 are identical, Fig. 35, which is the projection of Fig. 34 therefore represents the same configuration as Fig. 33.

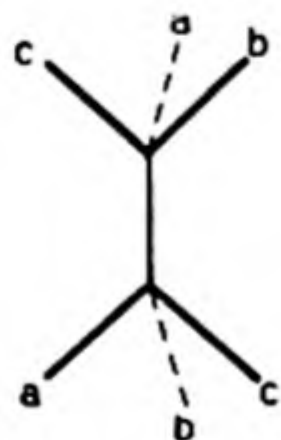


Fig. 34. Compound represented by Fig. 32, after rotation of upper atoms or groups

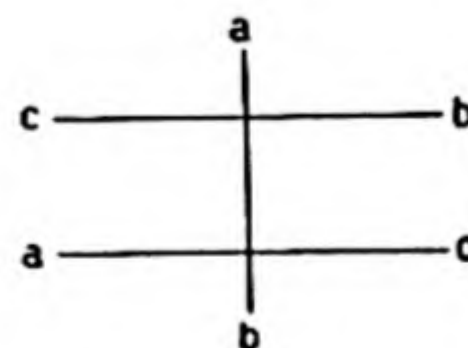


Fig. 35. Projection of Fig. 34

A rotation of the asymmetric carbon atoms with respect to each other in the space model corresponds in the projection figure with a displacement

of each of the groups *a*, *b* and *c* to the next position. The projection formulae of the tartaric acids are as follows:—

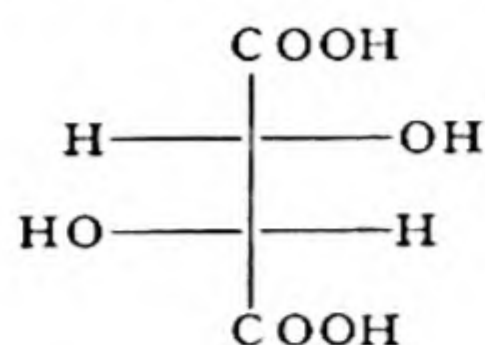


Fig. 36.

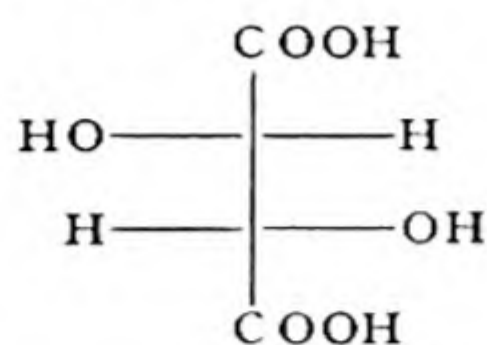
dextro-Tartaric acid

Fig. 37.

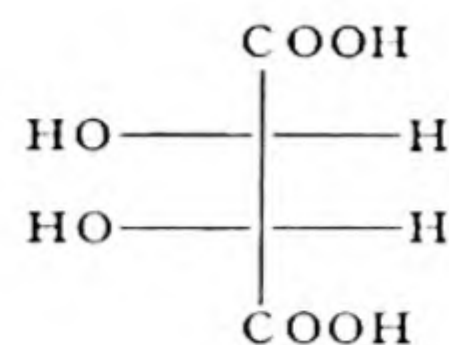
laevo-Tartaric acid

Fig. 38.

meso-Tartaric acid

Fig. 36 and Fig. 37 represent optical antipodes. The space models of optical antipodes are not superimposable. This is expressed in the projection formulae because those for the two antipodes cannot be superimposed by rotation in the plane of the paper. It is arbitrarily assumed that Fig. 36 represents the *dextro*-rotatory form.

135. *d*-Tartaric acid COOHCHOHCHOHCOOH .

This *dextro*-rotatory acid occurs in grape juice or must as the acid potassium salt COOKCHOHCHOHCOOH , which is sparingly soluble in water and very sparingly soluble in dilute alcohol. During fermentation of the juice, the salt settles out on the bottom of the vat along with the yeast. In order to prepare tartaric acid from this crude product, which is called *wine-lees* or *argol* (the purified salt is called *cream of tartar*), it is boiled with dilute hydrochloric acid, then milk of lime is added when the acid is precipitated as the calcium salt, calcium tartrate, $\text{CaC}_4\text{H}_4\text{O}_6$, and this is converted into the free acid by treatment with sulphuric acid.

Tartaric acid is readily soluble in water, less soluble in alcohol and insoluble in ether. It crystallises without water of crystallisation in large transparent crystals; the rotation of a 20 % solution at 20° is $+11.98^\circ$. On heating above the melting point (170°), it loses water and can be converted into various anhydrides depending on the temperature and the duration of heating. On heating to still higher temperatures, pyruvic acid (147) is formed and charring occurs. Tartaric acid can be converted into succinic acid by the action of certain bacteria.

Tartaric acid is used industrially as an ingredient of foodstuffs, for pharmaceutical purposes and in the textile industries. When potassium hydrogen tartrate is boiled with antimony oxide and water, *potassium antimonyl tartrate* or *tartar emetic*, $2[\text{KO}_2\text{CCHOHCHOHCO}_2(\text{SbO})] \cdot \text{H}_2\text{O}$, on account of its emetic properties, is produced.

A solution obtained by dissolving tartaric acid, copper sulphate and alkali (in excess) in water, is called *FEHLING'S solution*. This is a useful reagent for testing the reducing power of many compounds. Reducing substances like

aldehydes, monosaccharides (159) produce yellow-red cuprous oxide (or a hydrate) from the deep blue solution.

FEHLING'S solution contains an alkali cupri-tartrate, in which the copper atom has replaced the hydrogen atoms of the alcoholic hydroxyl groups (I):



This follows from the fact that a neutral solution containing a mol. of alkali tartrate can dissolve a mol. of cupric hydroxide. Alkali cupri-tartrates may be obtained in the crystalline state, *e.g.* $(\text{C}_4\text{H}_2\text{O}_6\text{Na}_2\text{Cu}) \cdot 2\text{H}_2\text{O}$. The solution contains the complex anion II; it does not give most of the reactions for copper ions and on electrolysis the copper-containing anion is transferred to the anode. The colour of FEHLING'S solution, which is much deeper blue than a solution of copper sulphate of equivalent concentration, also points to the presence of a complex copper-containing ion.

l-Tartaric acid is obtained from racemic acid. Except for the rotatory power, which is -11.98° for a 20 % solution at 20° , this acid has the same properties as its optical antipode.

136. Racemic acid and meso-tartaric acid. When *d*-tartaric acid is heated with water at 165° for several days, small quantities of racemic acid and meso-tartaric acid are produced. When a solution of sodium *d*-tartrate is boiled for some time with an excess of caustic soda, eventually it is converted completely into the sodium salt of racemic acid.

In this case it appears that meso-tartaric acid is first produced and this is then converted into racemic acid (HOLLEMAN). It may be seen from the projection formulae (on page 213), that for the conversion of *d*-tartaric acid into meso-tartaric acid it is necessary for a rearrangement of groups to occur around one carbon atom only. When *d*-tartaric acid is converted into its optical antipode a rearrangement on both asymmetrical atoms is necessary. Hence for the formation of racemic acid, half the molecules of *d*-tartaric acid must be converted into *l*-tartaric acid.

Racemic acid is produced by mixing sufficiently concentrated solutions of *d*- and *l*-tartaric acids; heat is evolved and the much more sparingly soluble racemic acid crystallises out (PASTEUR). From this it follows that racemic acid is to be considered as a molecular compound of *d*- and *l*-tartaric acids. In solution, racemic acid consists of a mixture of *d*- and *l*-forms as

appears from determinations of the depression of the freezing point. From a determination of the vapour density of esters of racemic acid it also follows that the vapour consists of a mixture of the optically active forms.

Racemic acid, which is found as a by-product in the preparation of tartaric acid from argol, crystallises with a molecule of water of crystallisation. It melts at 204° and differs in crystalline form from the active isomers. In addition, its salts have frequently a different content of water of crystallisation from the corresponding salts of the active acids. The sodium ammonium salts of *d*- and *l*-tartaric acids crystallise with four molecules of water of crystallisation; the corresponding salt of racemic acid however has only one molecule of water of crystallisation.

Meso-tartaric acid, which was discovered by PASTEUR in 1853, melts at 140° . The acid potassium salt is more readily soluble in cold water than the corresponding salts of the other tartaric acids. Tartaric acid, racemic acid and mesotartaric acid can be recognised micro-chemically by the crystalline form of the calcium salts. Calcium racemate is much more difficultly soluble in water than the calcium salts of the other acids, so that a solution of racemic acid gives a turbidity with a solution of calcium sulphate, whereas the other acids do not.

137. The views on the stereo-chemical structure of the tartaric acids is confirmed by the relationship, which exists between these acids and fumaric acid and maleic acid.

By oxidation in aqueous solution with potassium permanganate, or preferably with potassium chlorate and osmium tetroxide as catalyst, maleic acid is converted into meso-tartaric acid and fumaric acid into racemic acid. This can be explained by assuming that in the addition of two hydroxyl groups to maleic acid, either bond 1,1' or bond 2,2' in Fig. 39 is broken, by which the configurations represented by Figs. 40 and 41 are produced. The corresponding projection formulae are shown in Figs. 40a and 41a.

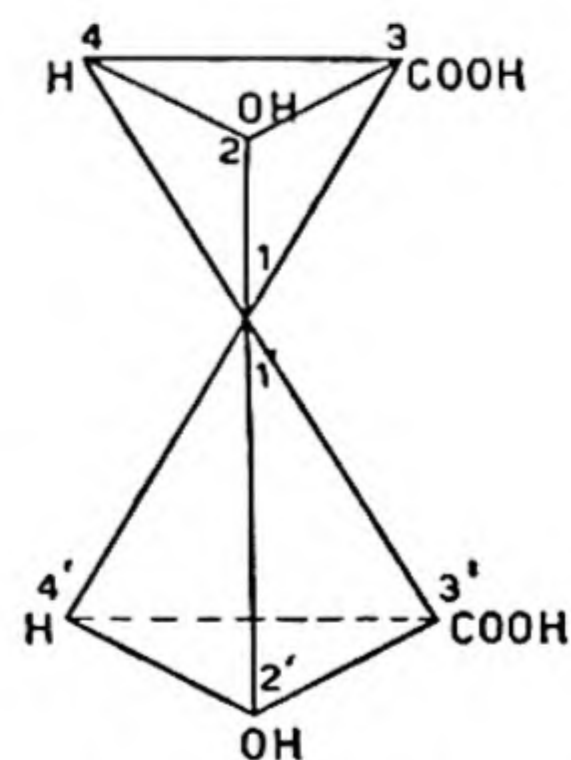
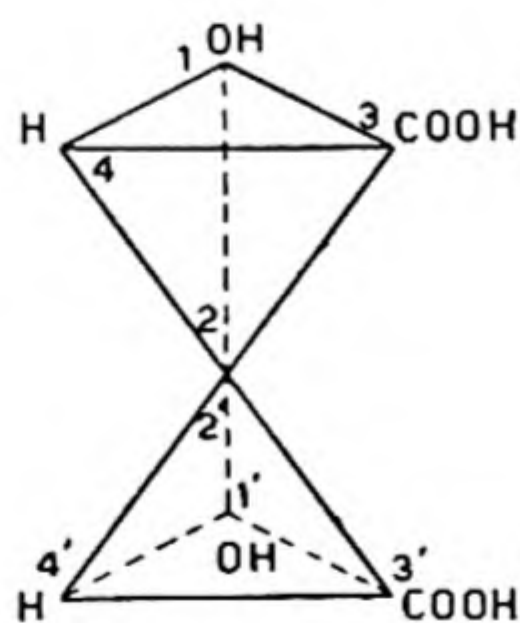
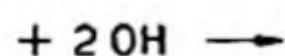
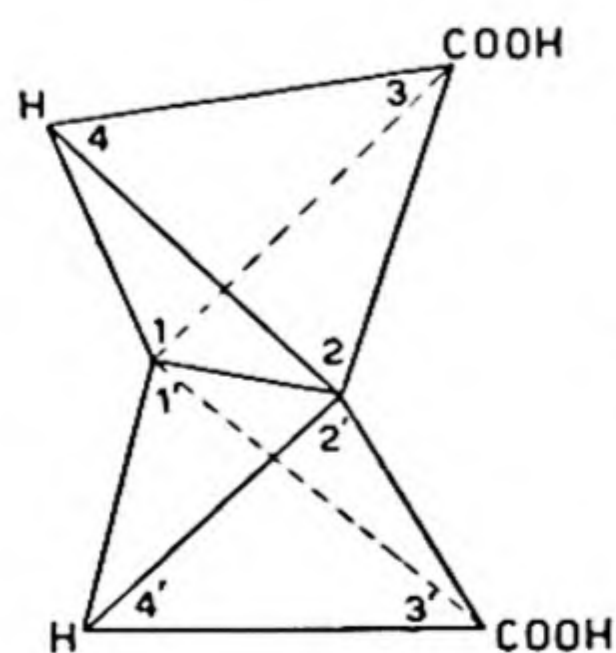


Fig. 39. Maleic acid

Fig. 40. *meso*-Tartaric acid

Fig. 41. *meso*-Tartaric acid

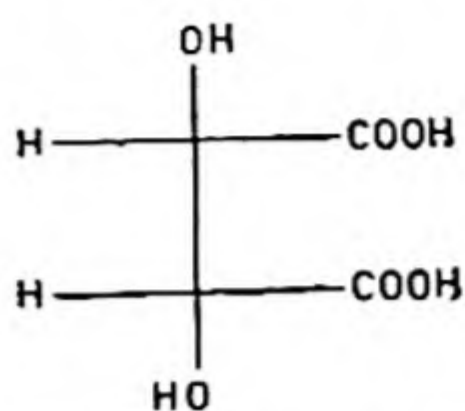


Fig. 40a. Projection of Fig. 40

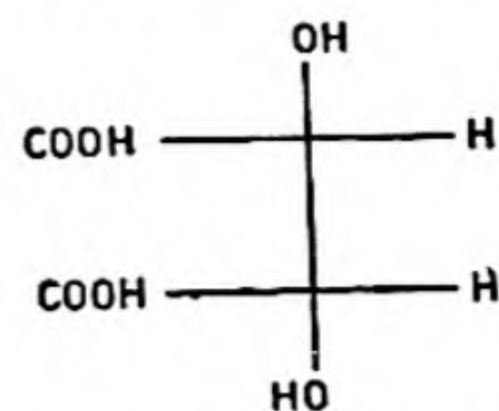


Fig. 41a. Projection of Fig. 41

Configurations 40a and 41a are identical, because when 40a is rotated in the plane of the paper through 180° , it coincides with 41a. This figure represents the configuration of *meso*-tartaric acid (see Fig. 38). Thus, in this way maleic acid gives rise solely to *meso*-tartaric acid.

In the addition of two hydroxyl groups to fumaric acid, two kinds of molecule are produced according to whether the bond 1,1' or 2,2' in Fig. 42 is broken; the configurations Fig. 43 and Fig. 44 are mirror-images, as is more clearly apparent in the projection formulae Figs. 43a and 44a. These are projection formulae of *d*- and *l*-tartaric acids, so that in this way dextro- and laevo-rotatory tartaric acids are produced from fumaric acid.

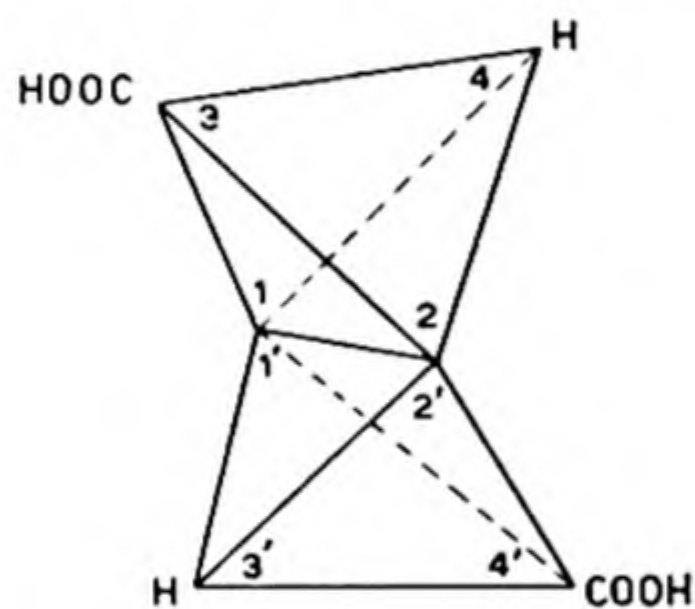


Fig. 42. Fumaric acid

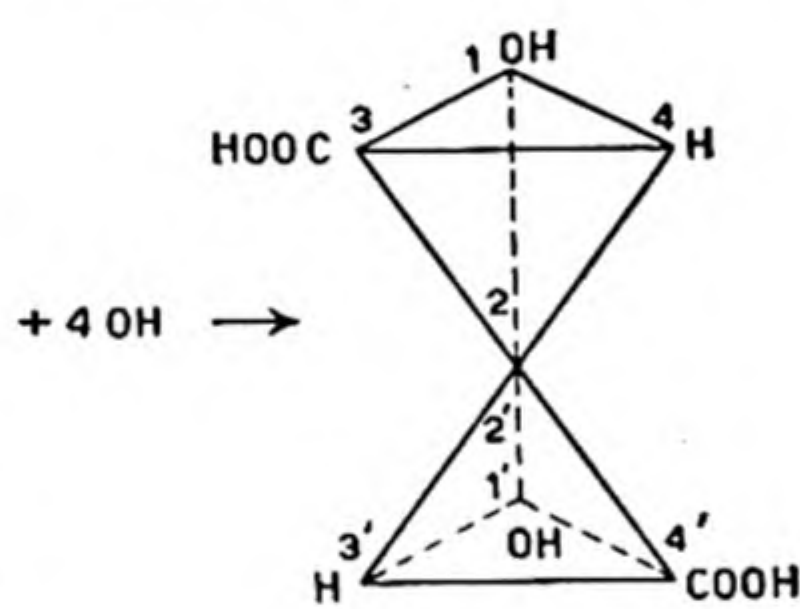


Fig. 43.

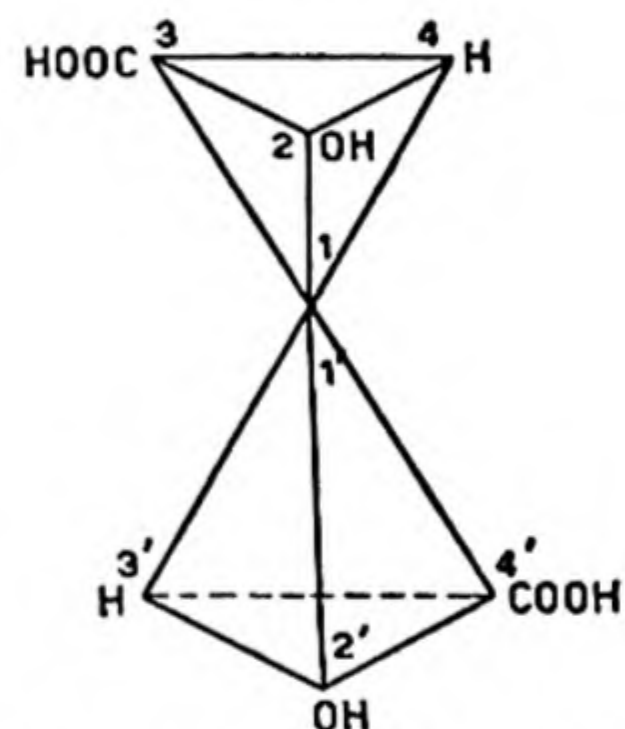


Fig. 44. Racemic acid

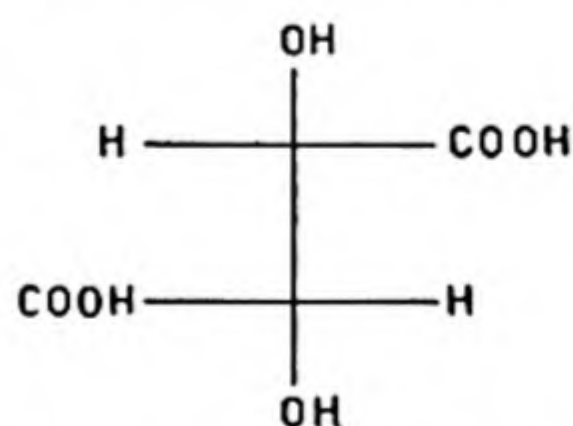


Fig. 43a. Projection of Fig. 43

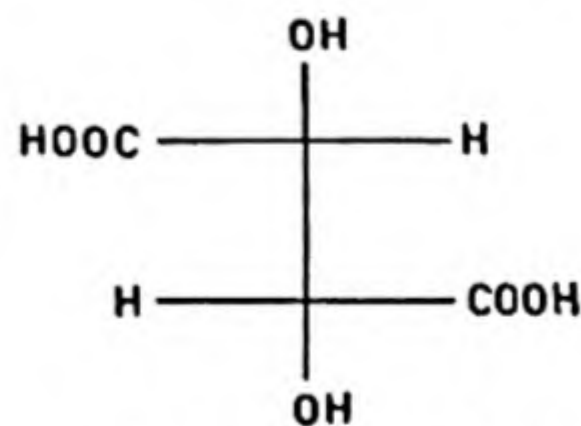


Fig. 44a. Projection of Fig. 44

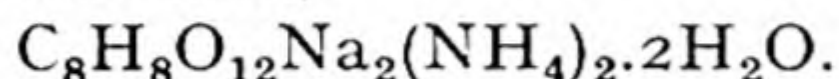
The addition of chlorine to neutral salts of fumaric and maleic acids in saturated sodium chloride solution is exactly similar to this addition of hydroxyl groups. 1,2-Dichloroethane 1,2-dicarboxylic acid, dichlorosuccinic acid (*meso*-form), is produced from maleic acid and *iso*-dichlorosuccinic acid,

the racemic form, which can be resolved into optical components, from fumaric acid.

The resolution of mixtures of optical antipodes (racemic mixtures)

138. Since optical antipodes have the same melting point and boiling point, the same solubility and vapour pressure, etc., (37), special methods must be used for separating a mixture of *d*- and *l*-forms.

The separation of an inactive mixture of optical antipodes into its optically active components was first carried out by PASTEUR (1850) on the sodium ammonium salt of racemic acid,



He found that two kinds of crystal separated when a solution of this salt was allowed to crystallise slowly, which could be differentiated by the occurrence of hemihedral surfaces. The visible hemihedral surfaces in Figs. 45A and 45B, are shaded and marked *a*. The crystalline forms behave like mirror images, which are not superimposable. PASTEUR was able to separate these two kinds of crystals by sorting them mechanically, *i.e.* by picking out the individual crystals of similar habit; one kind appeared to consist of the salt of dextro-rotatory tartaric acid and the other kind of the salt of laevo-rotatory tartaric acid. In this way two optical antipodes were obtained for the first time. PASTEUR also prepared *d*- and *l*-tartaric acids from these salts and these also form hemihedral crystals as shown in Figs. 46A and 46B.

Later on it was discovered (VAN 'T HOFF) that separate crystals of the *d*- and the *l*-tartrate separate from a solution of the sodium ammonium racemate only when the temperature is below 27°; when the solution is evaporated above this temperature a *racemic double salt* of the *d*- and *l*-tartrates separates. The transition point is 27°:

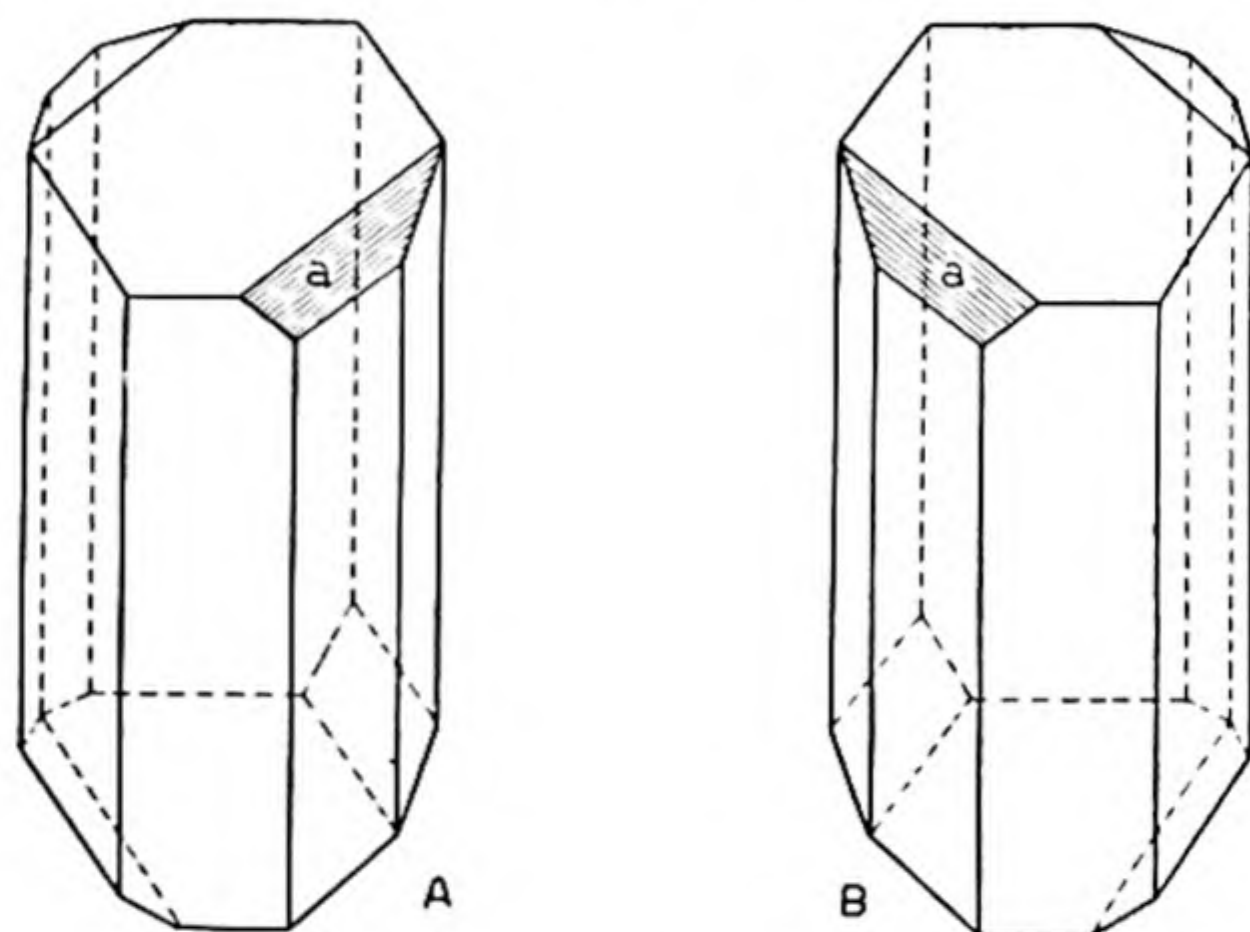


Fig. 45. Crystalline form of the sodium ammonium tartrates

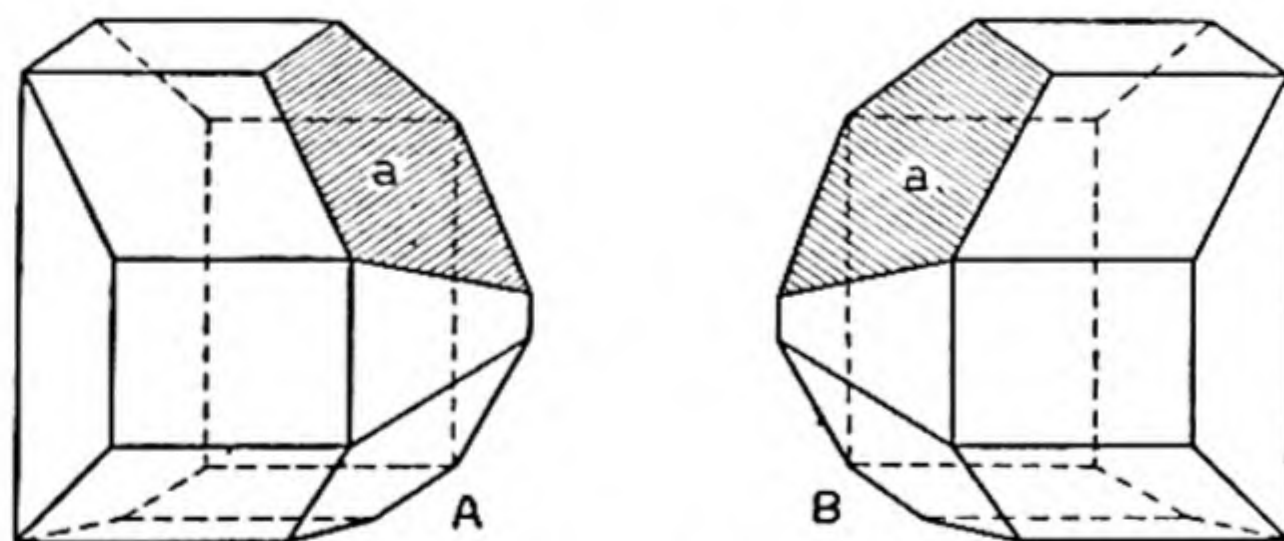
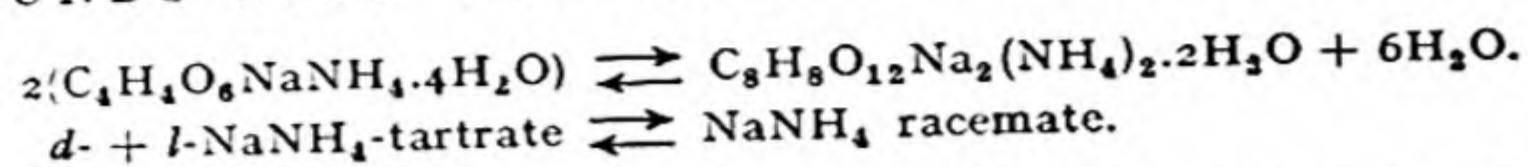


Fig. 46. *d*- and *l*-tartaric acids



Molecular compounds of two optical antipodes are called *racemic* compounds after the first discovered example, racemic acid. Racemic compounds exist only in the crystalline state. In liquid antipodes, in those cases which have been carefully examined, the same values have been found for the specific gravity, refractive index and viscosity for the mixture of equal quantities of the *d*- and *l*-forms, as for both antipodes separately. From this, it may be concluded that a molecular compound between the antipodes is not formed in the liquid state. Mixtures of equal quantities of *d*- and *l*-forms are referred to as *racemic mixtures* or as *d,l*-forms. When crystals are being dealt with the mixture is referred to as a *racemic conglomerate*.

A racemic compound and a racemic conglomerate may be distinguished in the following way. A saturated solution is made of the crystals (*d,l*-form) under examination, which is of course optically inactive. If the solid substance consists of a conglomerate of crystals of the *d*- and *l*-forms, the solution is saturated with regard to both forms; hence if the solution is shaken with crystals of the *d*- or *l*-form, nothing further passes into solution and the liquid remains inactive. On the other hand, if a racemic compound is being dealt with, the solution is not saturated with respect to the *d*- or *l*-form, some of which passes into solution and the liquid becomes optically active. (BAKHUIS ROOZEBOOM).

Cases are also known in which mixed crystals of the optical antipodes separate (*pseudo-racemic mixed crystals*).

The equality in *scalar properties* (solubility, melting point, specific gravity, vapour pressure, etc.) of optical antipodes is in accordance with the molecules of these substances behaving as mirror-images. In both kinds of molecules all the mutual distances between the atoms are identical. If however an atom or a group of atoms in these optical antipodes is replaced by a group of atoms containing an asymmetric carbon atom, the resultant molecules are no longer mirror-images of each other, so that the newly formed substances no longer have the same properties and may therefore be separated from each other, for example, by utilising a difference in solubility.

Thus a racemic mixture of optically active acids can be resolved by preparing salts with an optically active base and separating them by crystallisation. The alkaloids (352), which frequently give well defined crystalline salts, are available as optically active bases. Racemic acid can be split up into its components by means of the *d*-cinchonine salt, (359) since *d*-cinchonine *l*-tartrate is more sparingly soluble than *d*-cinchonine *d*-tartrate. (The optical antipode of *d*-cinchonine *d*-tartrate would be *l*-cinchonine *l*-tartrate). The optically active tartaric acids are obtained by decomposing the cinchonine salts. In the same way *d,l*-lactic acid can be resolved into its optical antipodes through the strychnine salts.

A racemic mixture of the *d*- and *l*-forms of an optically active base can be separated by preparing salts with an optically active acid. This second method of resolving racemic mixtures, which was also discovered by PASTEUR, is much more frequently employed than the method depending on the sorting of hemihedral crystals, since well-formed crystals can be obtained only in a few cases.

Optically active alcohols can be esterified with an optically active acid; the esters of *d*-alcohol with *d*-acid and of *l*-alcohol with *d*-acid can be separated. Also the velocity of esterification of *d*-acid with *l*-alcohol is different from that of *l*-acid with *l*-alcohol.

On heating *d,l*-mandelic acid (265) with the optically active alcohol, *l*-menthol, (295) for an hour, both active mandelic acids are partially converted into the menthyl esters; the remaining mandelic acid shows a laevo-rotation, from which it follows, that *d*-mandelic acid is esterified more quickly than *l*-mandelic acid by *l*-menthol.

In agreement with this, the menthyl ester gave mandelic acid with a dextro-rotation on hydrolysis (MARCKWALD and MACKENZIE).

Optical antipodes may show a different behaviour towards different kinds of moulds and bacteria and in biochemical reactions in general. This very important fact for biology was also discovered by PASTEUR, who based a method on it for obtaining one of the optical antipodes of a racemic mixture.

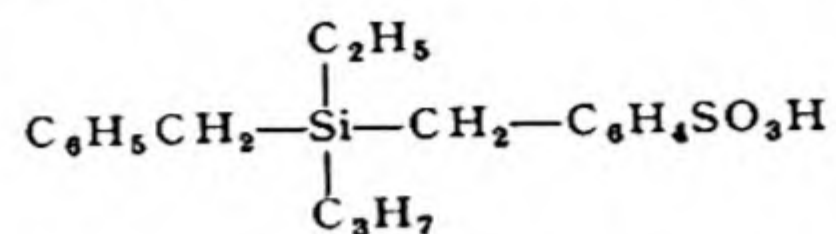
When *penicillium glaucum* is grown in a dilute solution of ammonium racemate, the solution becomes laevo-rotatory since ammonium *d*-tartrate is decomposed by the mould while the *l*-tartrate is not; the same mould decomposes *l*-lactic acid so that the *d*-form remains behind from a solution of *d,l*-lactic acid, *bacillus acidi laevolactici* however, decomposes the *d*-form of lactic acid.

In biochemical processes in which the action of micro-organisms on optically active substances play a part, the latter may react with constituents of the living cell, which themselves have an asymmetrical structure. The different behaviour of antipodes in a biochemical sense is therefore analogous to the difference in reactivity of antipodes in reactions with another optically active substance, mentioned above.

Optically active compounds in which the asymmetry depends on an atom of another element than carbon

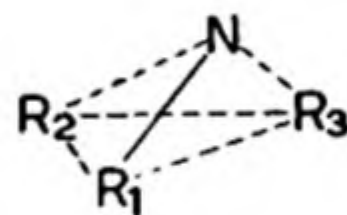
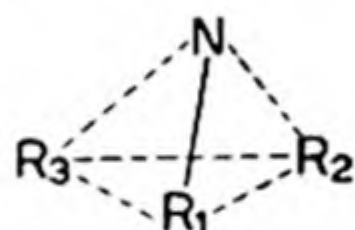
139. *Optically active silicon compounds.* Since the silicon atom has four valency electrons in the outer shell, the compound SiR_4 (52) has a tetrahedral structure like CR_4 . It is to be expected therefore, that a compound in which the silicon atom is attached to four different groups, would occur in optically active forms. An example of this has actually been found

220 COMPOUNDS WITH TWO OR MORE FUNCTIONAL GROUPS CH. 8
(CHALLENGER and KIPPING). The *d,l*-form of this tetra-substituted silane



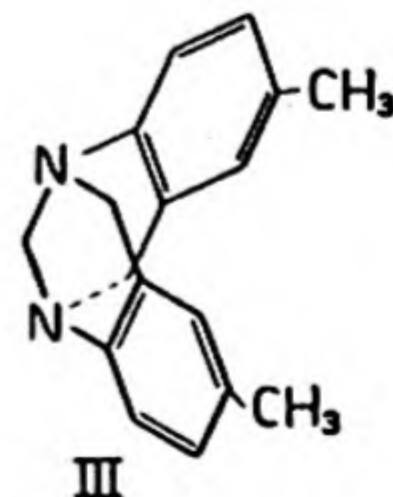
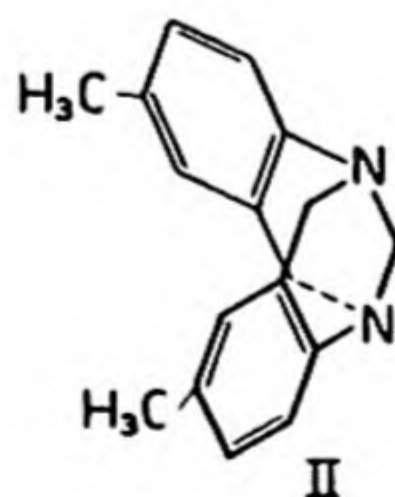
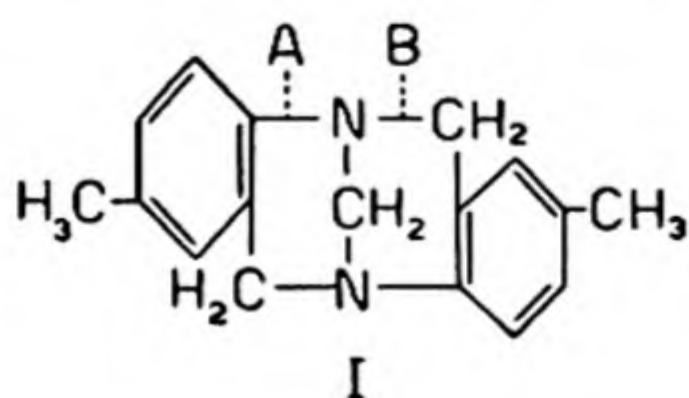
was resolved into its optical components through the brucine salts.

Optically active ammonium compounds. From the dipole moment of ammonia ($\mu = 1.44$) and from an examination of the infra-red spectrum it has been concluded that the hydrogen atoms and the nitrogen atom in NH_3 do *not* lie in one plane, but that this molecule has a pyramidal structure in which the N-atom occupies the top and the hydrogen atoms the three corners of the base of the pyramid. The angles between the N—H bonds are 107° ; the distance between N and H is 1.02 \AA . Since the amines have been found to possess dipole moments, *e.g.* $\mu = 1.31$ for CH_3NH_2 , $\mu = 0.96$ for $(\text{CH}_3)_2\text{NH}$, and $\mu = 0.70$ for $(\text{CH}_3)_3\text{N}$, it is assumed that these compounds also possess a pyramidal structure. It would be expected therefore that it should be possible to split tertiary amines of the type $\text{NR}_1\text{R}_2\text{R}_3$ into optically active components, since two mirror-image forms can be set out for such molecules.



Notwithstanding many attempts with this end in view, no one has yet succeeded in obtaining such tertiary amines in optically active forms. It is assumed therefore that optically active compounds of this type racemise very quickly, because the N-atom can take up two positions *viz.* above and below the plane $\text{R}_1\text{R}_2\text{R}_3$. (MEISENHEIMER; KETELAAR).

This mode of racemisation will not occur when a nitrogen atom forms part of two rings, as is the case in compound I below (TRÖGER's base). This substance can be obtained by condensation of *p*-toluidine with formaldehyde with the elimination of water. The heterocyclic rings A and B, occurring in this molecule, cannot lie in one plane, since this would produce too great a strain. When a strain-free space model is constructed, it appears that two noncongruent mirror-images (II and III) are possible, which correspond with two optical antipodes.

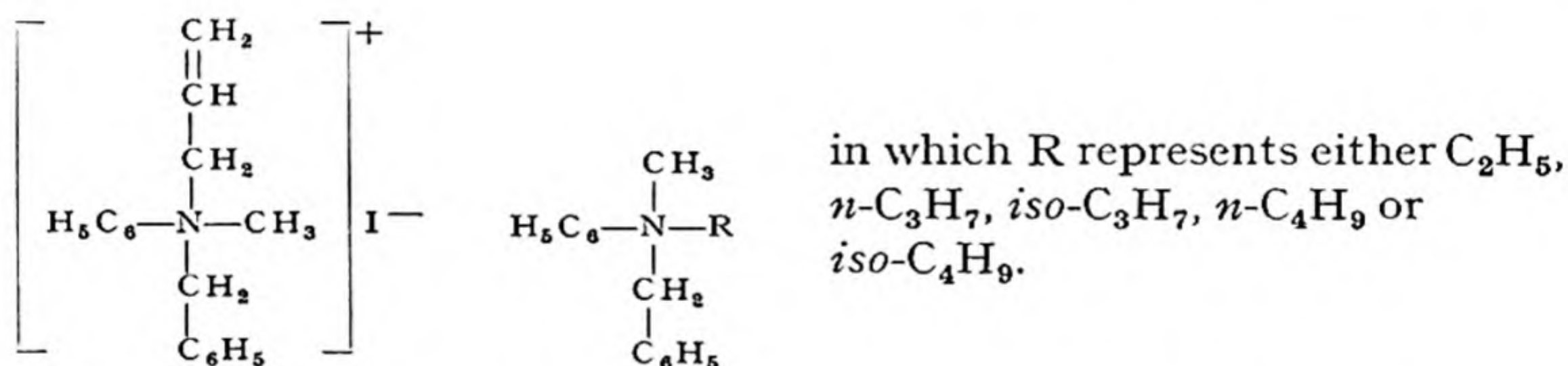


The tertiary amine grouping $\text{NR}_1\text{R}_2\text{R}_3$ occurs twice in the molecule. The amine nitrogen atom is situated at the top of a three sided pyramid; the corners of the base of this pyramid are occupied by three different groups. In fact PRELOG and WIELAND succeeded in resolving this base into optical components in 1944. For this purpose they used a new method of resolution which is an extension of the method of chromatographic adsorption (308).

A solution of the *d,l*-base in light petroleum is allowed to flow through a column of finely powdered milk-sugar (*d*-lactose) on which it is adsorbed.

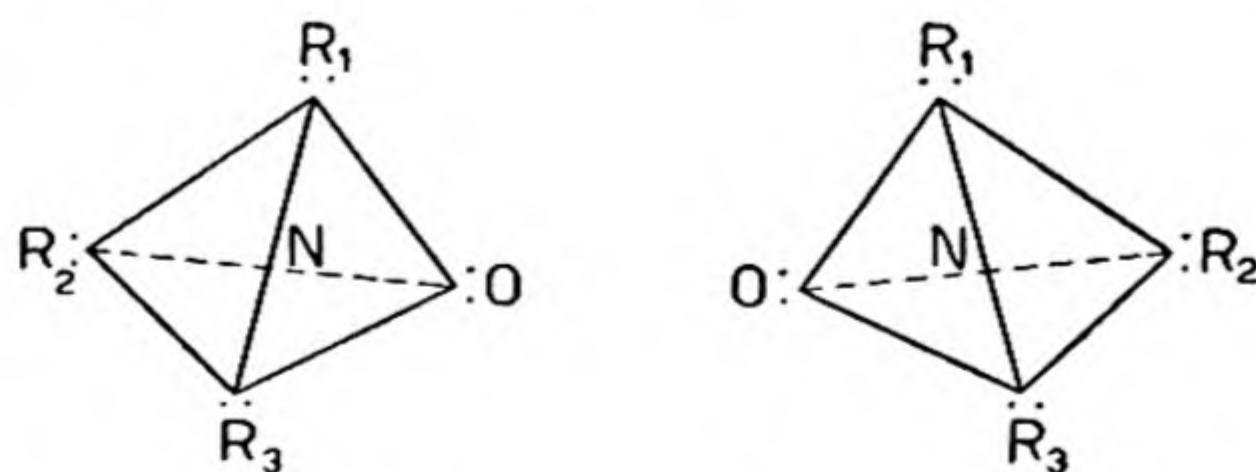
By fractional elution with light petroleum the first fractions obtained from the filtrate contain mainly the *d*-base and the later fractions contain the *l*-base. This separation depends on the fact that of the two antipodes one is adsorbed more firmly than the other on the asymmetric adsorbent.

In the quaternary ammonium ions (47) of the type $(\text{NR}_4)^+$ it is assumed that the four groups of atoms are arranged tetrahedrally around the nitrogen atom. It would be expected therefore, that quaternary ammonium salts of the type $[\text{NR}_1\text{R}_2\text{R}_3\text{R}_4]\text{X}$ should be resolvable into optically active components. Many examples of such cases are known (POPE and PEACHY; JONES), *e.g.*:



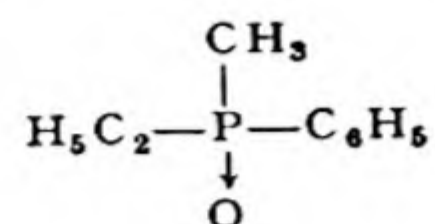
Another proof of the tetrahedral arrangement of the N—C bonds in quaternary ammonium salts is given in 332.

Optically active amine-oxides. The spatial configuration of the amine-oxides $(\text{R}_3)\text{NO}$ (49) is similar to that of the tetra-alkylammonium ion. The three groups R and the oxygen atom are arranged tetrahedrally around the nitrogen atom. An amine-oxide in which the groups R are different from one another, can occur therefore, in two mirror-image forms.



It has indeed been possible to resolve the amine-oxides $(\text{CH}_3)(\text{C}_2\text{H}_5)(\text{CH}_2=\text{CHCH}_2)\text{NO}$ and $(\text{CH}_3)(\text{C}_2\text{H}_5)(\text{C}_6\text{H}_5)\text{NO}$ into their optical components through the *d*-bromocamphor sulphonates (MEISENHEIMER).

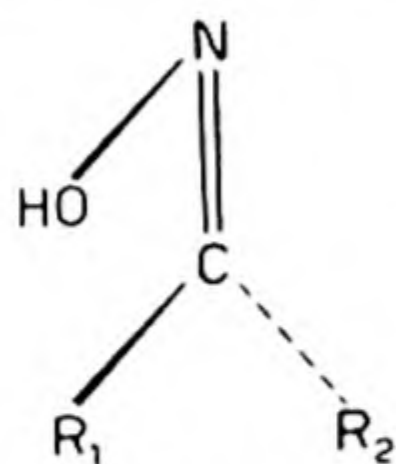
It has also been possible to obtain phosphine-oxides (51) like methylethylphenylphosphine-oxide,



in optically active forms.

These compounds must be similar in structure to the amine-oxides. *Optically active arsenic compounds* are also known.

140. Cis-trans isomerism in oximes. According to a theory proposed by A. WERNER and A. HANTZSCH in 1891, the stereochemical structure of an oxime may be represented as annexed.

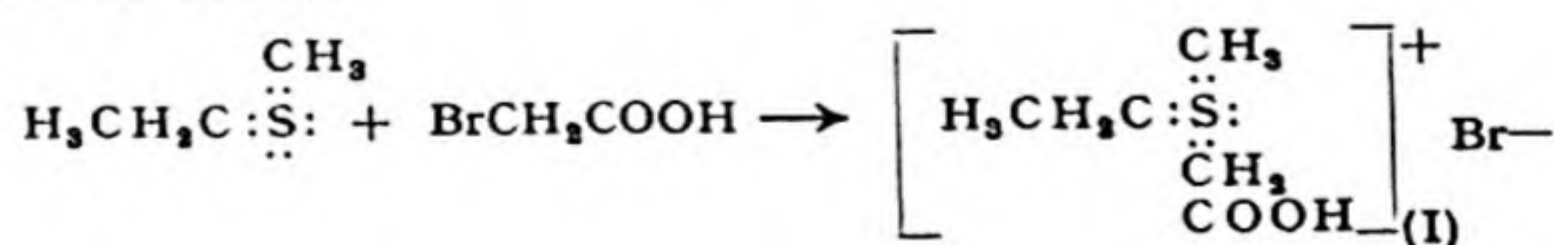


The double bond between N and C lies in the plane of the paper, while the bond between N and HO lies either in front of or behind the plane of the drawing. This stereochemical model is in agreement with views on the stereochemical structure of the amines. The bonds C—R₁ and C—R₂ lie in a plane perpendicular to the plane of the paper, so that group R₂ will lie in front and group R₁ behind this plane. It is clear that when groups R₁ and R₂ are dissimilar, two stereoisomeric forms can occur which are to be considered as *cis*- and *trans*-forms like those met with in the *cis-trans*-isomerism of ethene derivatives. Examples of *cis-trans*-isomers in oximes are discussed in 259.

Cis-trans-isomers in azobenzene (249) and diazo-compounds (248) may be explained in a similar way.

The stereochemical structure of hydrogen cyanide and the carbonitriles is similar to that of the alkynes. The directions of the bonding forces of the triple bond between C and N lie in one plane. The single bond between C and H or between C and R lies in the same plane. Hence hydrogen cyanide has a linear structure H—C≡N, like ethyne (acetylene).

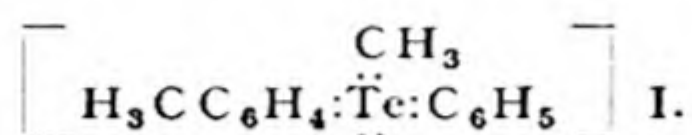
141. Optically active sulphur-compounds. The structure of the sulphonium ion (44) in space, can be so represented that the sulphur atom is situated at the centre of a tetrahedron. Three of the corners are occupied by groups of atoms and the fourth by a pair of electrons. If the three groups of atoms are all different from one another, then an asymmetric structure is produced. Indeed it has been possible to prepare such a sulphonium compound and to resolve the *d,l*-form into optically active components (W. J. POPE, 1900).



Methylethylcarboxymethylsulphonium bromide, I, which consisted of the *d,l*-form, was converted by means of silver *d*-camphorsulphonate (C₁₀H₁₅O)OSO₂Ag into a mixture

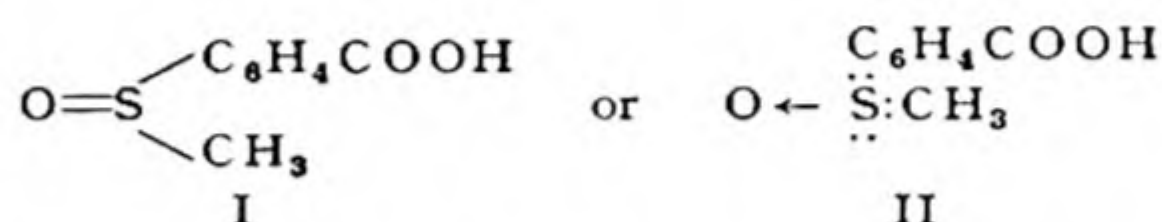
of stereo-isomeric sulphonium salts of this acid. In this reaction the Br in compound I was replaced by the asymmetrical anion $(C_{10}H_{15}O)OSO_2$. *d*-(Methylethylcarboxymethylsulphonium)-*d*-camphorsulphonate was eventually isolated by repeated recrystallisation of the mixture of sulphonium *d*-camphorsulphonates. After replacing the anion of the camphorsulphonic acid by an optically inactive anion, a dextro-rotatory sulphonium salt is obtained in which the sulphonium cation is the seat of the optical activity.

In a similar way, *ternary selenium and tellurium salts, e.g.,*



have been obtained in optically active forms.

It is also noteworthy that a *sulphoxide* has been prepared in optically active forms by KENYON and PHILIPS, viz.:



This cannot be explained on the classical formula I with a doubly bound oxygen atom but it is clear from the electronic formula II.

The determination of the stereochemical configuration of optically active compounds

142. For the absolute determination of the configuration of two optically active antipodes it would be necessary to know which of the two space models represents the laevo-rotatory form and which the dextro-rotatory form; this is not yet possible.

Although many researches have been directed towards finding the relationship between the size and the sign of the optical rotation and the nature of the groups, which are arranged about the asymmetric carbon atom, it is as yet impossible to give generally valid rules for this purpose.

It is, however, possible to decide whether two different compounds, each of which contain one or more asymmetric carbon atoms, have a similar configuration. This *method for determining the relative stereochemical configuration*, which has been employed in a number of cases by FREUDENBERG, for example, will be illustrated by a few examples. Before doing so, a remark must be made on the connection between rotatory power and configuration. There might be a tendency to assume that compounds with a similar configuration around the asymmetric carbon atom should agree in rotatory power; this is not the case however.

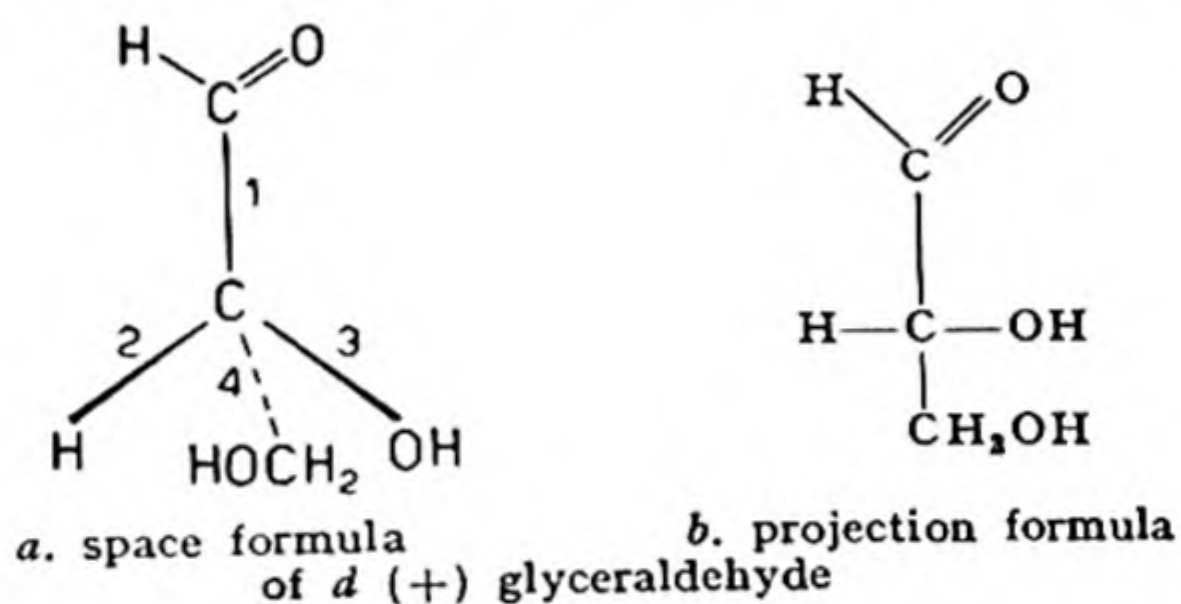
Amyl alcohol, obtained by fermentation, is laevo-rotatory, its acetate is dextro-rotatory; the laevo-rotatory alcohol is recovered when the dextro-rotatory ester is hydrolysed. Natural tartaric acid is dextro-

rotatory like dimethyl tartrate. The dimethyl ester of *diacetyltartaric acid*, $\text{H}_3\text{COOCCHO}(\text{COCH}_3)\text{CHO}(\text{COCH}_3)\text{COOCH}_3$, however, is laevo-rotatory.

Both the absolute magnitude and the sign of the optical rotation are influenced very strongly by the nature of the groups arranged around the asymmetric carbon atom. Hence it is not possible to conclude whether or not two asymmetric compounds have a similar configuration by comparing the rotatory powers. To do this, use must be made of suitably chosen chemical reactions.

Dextro-rotatory glyceraldehyde is chosen as the starting point. This compound was obtained by WOHL and MOMBER by a method of synthesis which allowed of its resolution into optical antipodes. The configuration given below was then allotted arbitrarily to the dextro-rotatory glyceraldehyde, which was designated as *d*(+)-glyceraldehyde, the letter *d* (dexter) referring to the configuration and the + sign indicating that the substance is dextro-rotatory.

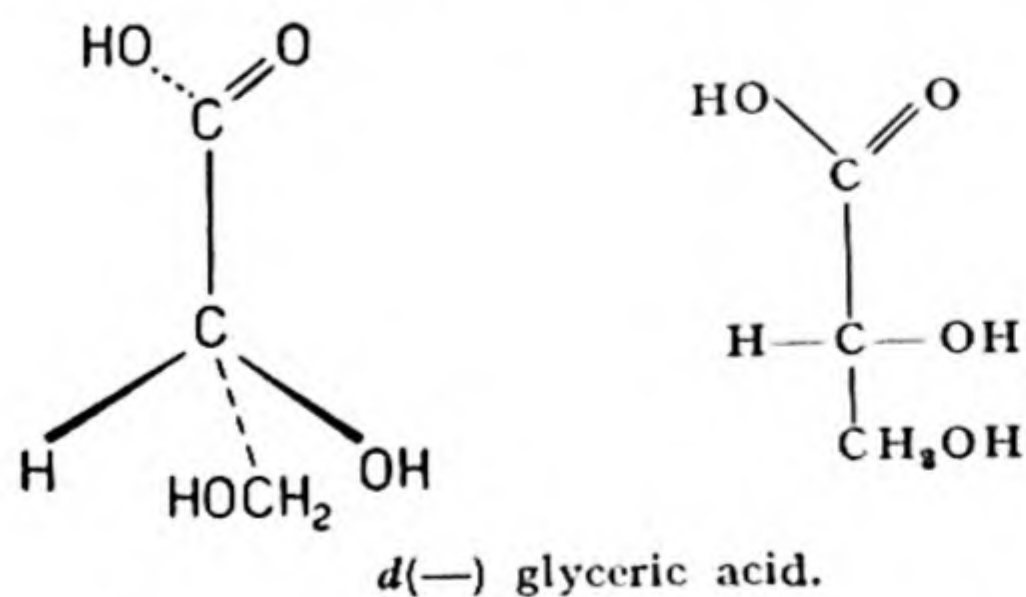
In *a* the thinly drawn line (1) lies in, the dotted line behind, and the thick lines (2 and 3) in front of the plane of the paper. In agreement with a proposal made by E. FISCHER (compare 134) the lines



lying in front of the plane of the paper are represented by horizontal lines in the projection formula *b*; lines which lie in or behind the plane of the paper are placed along the vertical in *b*.

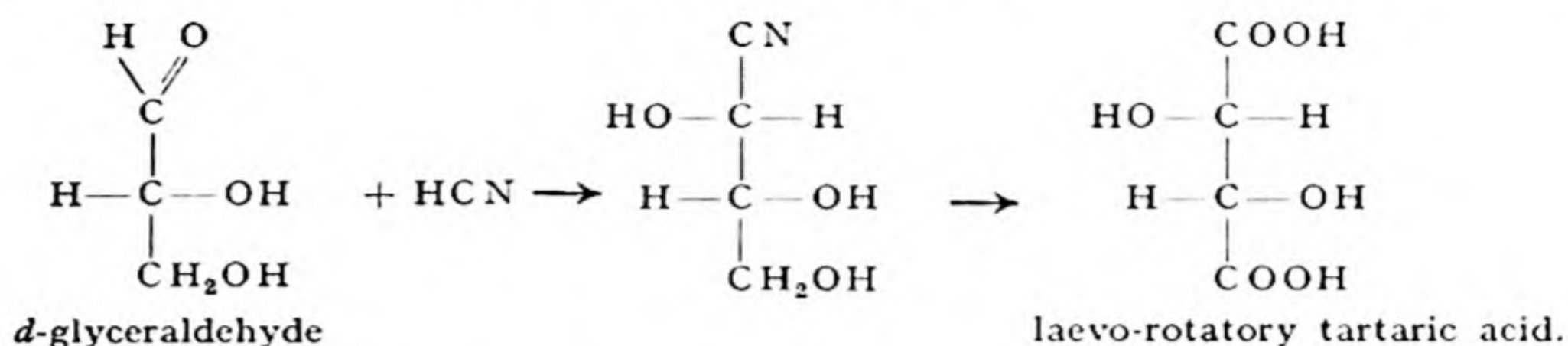
On oxidation of dextro-rotatory glyceraldehyde an optically active glyceric acid is produced, which is laevo-rotatory. In this oxidation the H-atom in the aldehyde group is replaced by an OH-group. Thus this replacement has *not* taken place on the asymmetric carbon atom; therefore there is no rearrangement of groups about this carbon atom (compare 143). It is

assumed therefore that laevo-rotatory glyceric acid has the same configuration as *d*(+)-glyceraldehyde and it is therefore designated *d*(—) glyceric acid.



By applying the cyanhydrin synthesis followed by hydrolysis of the CN-group and oxidation of the CH_2OH -group, laevo-rotatory tar-

taric acid is produced along with meso-tartaric acid from *d*-glyceraldehyde, so that the following configuration is given to laevo-tartaric acid:

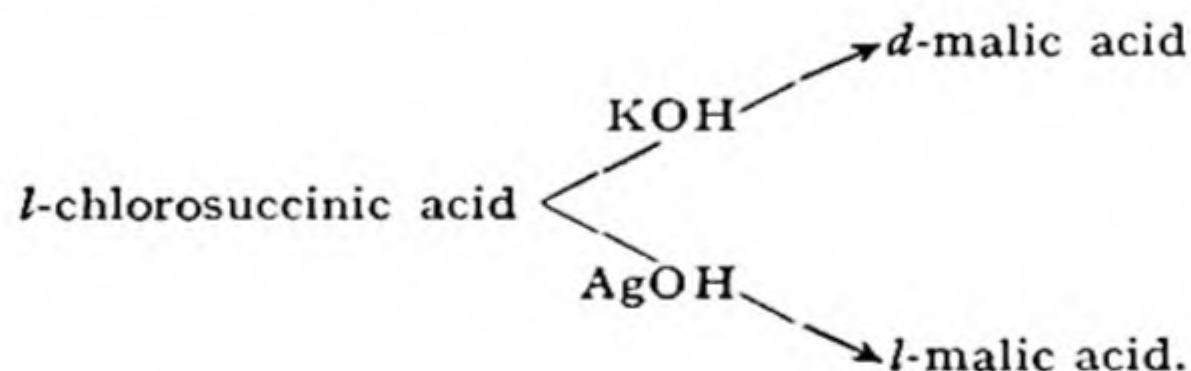


Thus laevo-rotatory tartaric acid should be designated *d*(-)-tartaric acid; since, however, dextro-rotatory tartaric acid, occurring widely distributed in the vegetable kingdom, has been called *d*-tartaric acid since olden times, the prefix *d*- is retained for this compound and the two optically active tartaric acids are designated as follows:



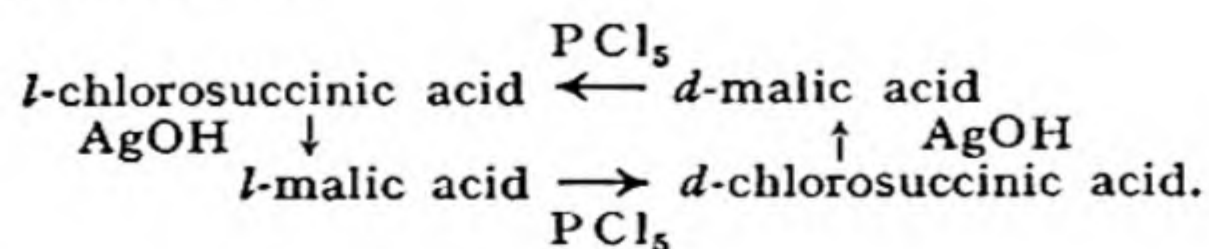
The Walden inversion

143. In the conversion of optically active halogeno-acids into hydroxy-acids, optically active acids of opposite rotation can be obtained depending on the reagent used. This phenomenon was discovered by P. WALDEN. From *l*-chlorosuccinic acid he obtained *l*-malic acid by the action of moist silver oxide and *d*-malic acid by the action of potassium, sodium or ammonium hydroxides:

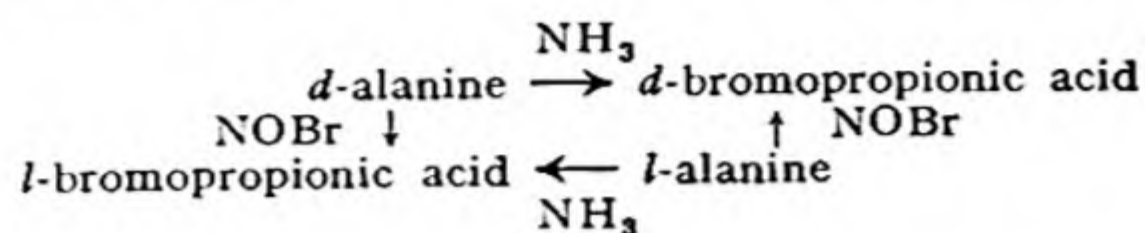


In one of these reactions a rearrangement of the groups around the asymmetric carbon atom must have taken place. It cannot be decided whether this happens during the action with KOH or during the reaction with AgOH.

WALDEN was able to convert *l*- and *d*-chlorosuccinic acids one into the other, at will, by the following reactions:



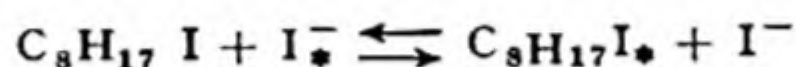
Thus in this cycle of reactions an alteration in the arrangement of the groups around the asymmetric carbon atom has taken place twice. This alteration, which occurs during a substitution reaction, is called the WALDEN *inversion*. Examples of this are found in various classes of compounds, *e.g.* in the reactions of amino-acids (E. FISCHER).



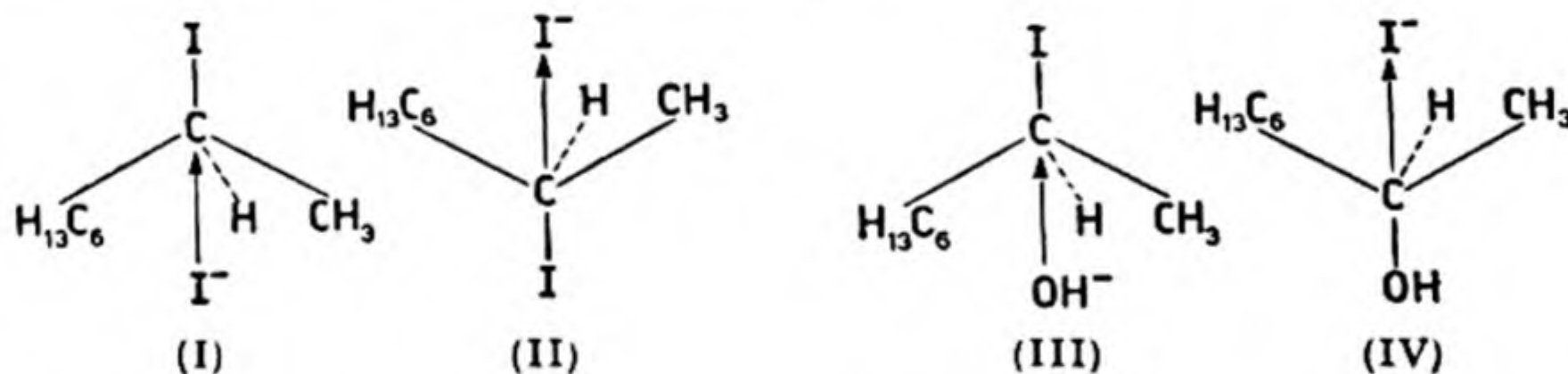
In these successive reactions an optically active substance is converted into its optical antipode without a racemic mixture being produced as an intermediate product.

Of the various researches from which an insight into the mechanism of the WALDEN inversion can be obtained, the following will be mentioned.

An optically active alkyl iodide, *e.g.* *d*-sec. octyl iodide $(\text{CH}_3)(\text{C}_6\text{H}_{13})\text{CHI}$, undergoes racemisation in a solution of sodium iodide in acetone; this racemisation goes parallel with an exchange between an iodide-ion and the iodine atom combined in the octyl iodide. This is shown by carrying out the experiment with sodium iodide containing a certain proportion of a radioactive isotope of iodine I_* ; after some time the isolated octyl iodide contains radioactive iodine. In this way the velocity of the exchange reaction:



can be measured. This velocity is found to be the same as the velocity of racemisation of *d*-sec.octyl iodide under the influence of iodide-ions. From this it follows that racemisation is connected with a replacement. On the basis of calculations, it is assumed that the iodide-ion approaches the octyl iodide molecule on the positive side of the dipole $\text{C}(+) - \text{I}(-)$. The iodide-ion becomes attached as an iodine atom, while the iodine atom originally present is repelled as an ion. From the figures given below it is clear that this goes parallel with a change in the configuration.

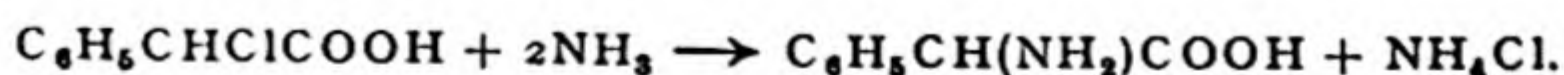


Since the exchange between iodine atom and iodide-ion is reversible, configuration (II) can, in the same way, change over into (I), so that finally a racemic mixture is produced.

However, if the iodine atom in the alkyl iodide is replaced by a hydroxyl-group, *e.g.* by the action of potassium hydroxide, a corresponding mechanism can be assumed, in which an OH^- ion approaches the alkyl iodide molecule on the positive side of the dipole $\text{C}(+) - \text{I}(-)$ (III).

Since the replacement of I by OH under these conditions is not reversible, configuration (IV) remains in existence, so that a WALDEN inversion takes place.

In this connection it should be mentioned that the occurrence or non-occurrence of a WALDEN inversion depends on the experimental conditions, which are not yet susceptible to a theoretical treatment. Thus *d*-aminophenylacetic acid is produced from *l*-phenylchloroacetic acid by treatment with dilute ammonia, but *l*-aminophenylacetic acid by adding liquid ammonia (SEETER):



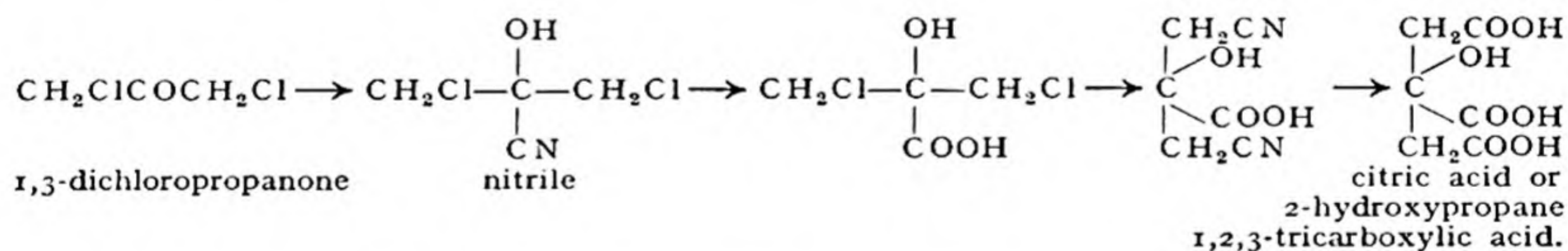
It is not possible to predict whether or not a WALDEN inversion will occur in a

particular reaction. It is found by experience that the occurrence of the WALDEN inversion is limited to those reactions in which direct replacement on the asymmetric carbon atom takes place. If a replacement in an optically active compound takes place in such a way that the valency bonds radiating from the asymmetric carbon atom are not concerned, then experience shows that the arrangement of the groups around the asymmetric carbon atom is unaltered.

(d) *Polybasic hydroxy-acids*

144. Of these acids only the tribasic acid, *citric acid*, $C_6H_8O_7$, is mentioned. This acid occurs in various fruits, *e.g.* in lemons to the extent of 6—7 %, in apples, berries, etc. It is prepared from the juice of unripe lemons. From this material sugar is first removed by fermentation and then the citric acid is separated as the calcium salt, which is readily soluble in cold water but very sparingly soluble in hot. Another technical method of preparing citric acid is by the action of certain species of mould (*citromyces*) on glucose, a 50 % yield of citric acid being obtained.

The structure of citric acid follows from the following synthesis (GRIMAUX). 1,3-Dichloropropanol-2 is converted into 1,3-dichloropropanone by oxidation; after addition of hydrogen cyanide and hydrolysis of the nitrile so obtained, this ketone gives a hydroxy-acid, from which a dinitrile is produced by treatment with potassium cyanide; this dinitrile is converted, on hydrolysis, into citric acid, *2-hydroxypropane 1,2,3-tricarboxylic acid*:



Triethyl citrate can react with acetyl chloride with the formation of an acetyl compound showing that the acid contains an alcoholic hydroxyl group. Citric acid is readily soluble in water and alcohol, crystallises with one molecule of water of crystallisation and melts at 153° when anhydrous. It is used for the preparation of lemonade and cordials and also in calico printing.

(viii) POLY-ALDEHYDES AND POLY-KETONES

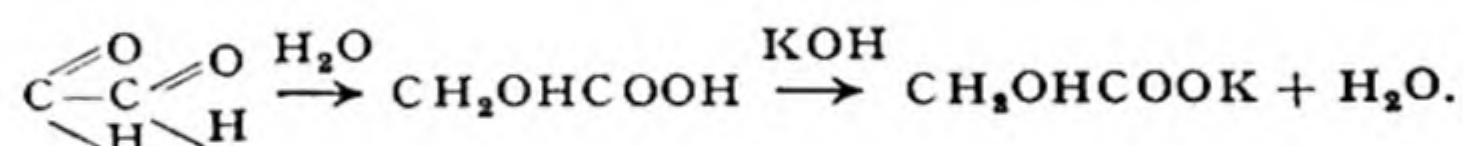
145. The simplest poly-aldehyde is the dialdehyde *glyoxal* or *ethanedial*, which is built up of two aldehyde groups, CHOCHO .

This compound can be prepared by the slow oxidation of ethyl alcohol with dilute nitric acid, when glycollic acid, oxalic acid and other products are produced as well as glyoxal. Glyoxal is also produced by the action of ozone on acetylene. Ethanediol is obtained in the form of a polymer, as a colourless, amorphous mass, which if still moist very easily dissolves in water, but after drying in vacuo at 110° it passes into solution only very slowly and then behaves like the monomeric compound. On distilling the polymer with phosphorus pentoxide, an emerald green gas is formed, which condenses on powerful cooling to yellow crystals, which become colourless on cooling still further. These crystals melt at 15° to a yellow liquid boiling at 51° . This is monomolecular ethanediol, which is very unstable. Traces of water produce the polymer, which can be depolymerised again by boiling with acetic anhydride.

Ethanediol is the simplest coloured compound consisting only of carbon, hydrogen and oxygen.

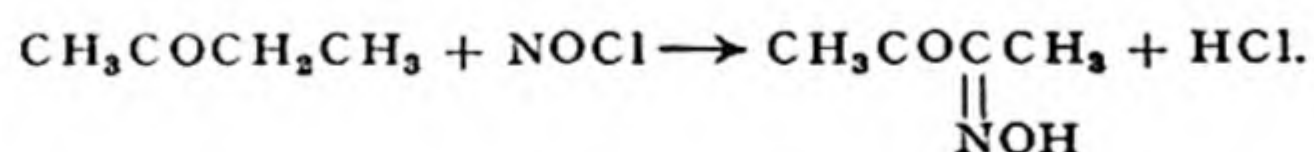
It shows all the reactions of aldehydes (59). Its structure as a difunctional aldehyde follows from the addition of two molecules of sodium bisulphite, from the formation of a dioxime and from the formation of oxalic acid by taking up two atoms of oxygen.

On treating ethanediol with potash, a molecule of water is taken up with the formation of the potassium salt of hydroxymethane carboxylic acid (glycollic acid). This is an example of the CANNIZZARO reaction (61):



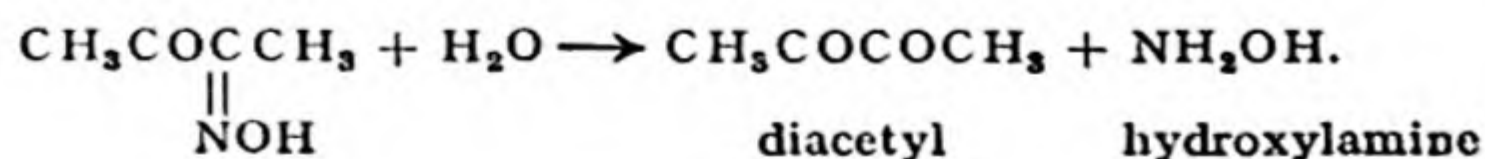
146. Diones, diketones. Substances in which two carbonyl groups occur, are classified as 1,2-, 1,3-, 1,4-diketones, etc.

1,2-Diones are obtained by the interaction of amyl nitrite and a little hydrochloric acid on ketones. Nitrosyl chloride NOCl, is first produced, which reacts on the ketone, *e.g.* butanone, with the formation of an *isonitrosoketone* and hydrochloric acid, the oxime grouping taking the place of a hydrogen atom in the CH_2 -group situated next to the carbonyl group:



Isonitrosoketones are produced also by the action of nitrous acid on ketones; they are decomposed, however, by an excess of nitrous acid, hence the former method of preparation is to be preferred.

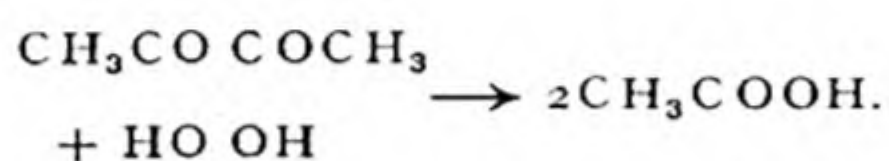
The diketone, butan-2,3-dione, *diacetyl* $\text{CH}_3\text{COCOCH}_3$, is obtained from the oxime along with hydroxylamine, by boiling with dilute sulphuric acid:



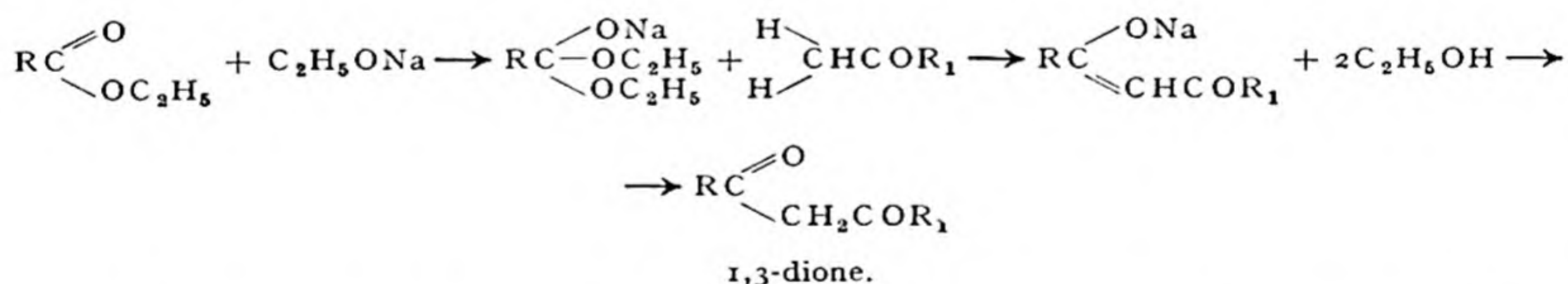
Keto-aldehydes, containing the group —COCHO , can be made in a similar way.

Diacetyl is a yellow liquid soluble in water, b.p. 80° , spec. grav. 0.973 at 20° . The dioxime derived from it, *dimethylglyoxime*, is a sensitive reagent for nickel ions, it forms a red nickel compound insoluble in water. Diacetyl occurs in very small quantities in butter and is mainly responsible for its flavour (VAN NIEL, KLUYVER and DERX).

Diacetyl adds on two molecules of hydrogen cyanide, gives a mono- and a di-oxime and behaves exactly like a substance with two carbonyl groups. A quantitative yield of acetic acid is produced by the action of hydrogen peroxide. From this it follows that the two carbonyl groups are situated next to one another:

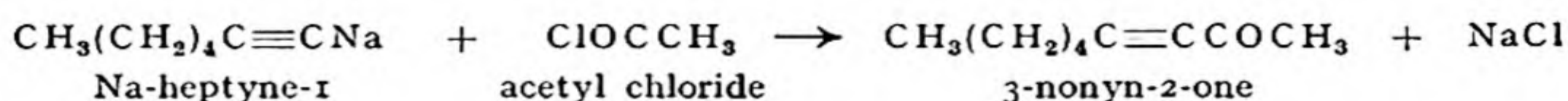


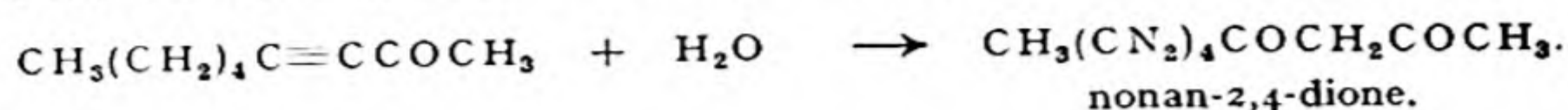
1,3-Diones. These substances are prepared by the method of CLAISEN and WISLICENUS, which is widely applicable and consists of condensing ketones with esters in the presence of sodium ethylate as condensing agent. Sodium or sodamide may be used for the same purpose. CLAISEN represented the course of the reaction in such a way that an intermediate addition product is formed, which is not isolated; this then reacts with a ketone RCOCH_3 containing a methyl group, in such a way that two molecules of alcohol are eliminated with the formation of a condensation product:



By the action of dilute sulphuric acid a substance should be produced with an OH-group attached to a doubly bound carbon atom; however, the grouping HO—C=CH— passes over into $\text{—COCH}_2\text{—}$ with the production, in this case, of a 1,3-dione.

1,3-Diones can also be obtained in the following way. By the action of an acid chloride on the sodium derivative of an alkyne, an unsaturated ketone is obtained, which takes up water, under the action of concentrated sulphuric acid, with the production of a dione:





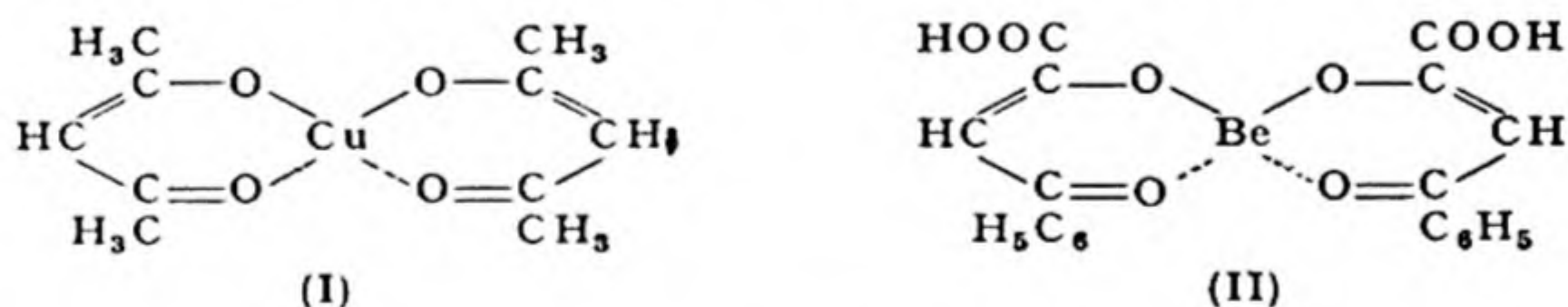
It is found that in diones which contain a methene group situated between two carbonyl groups, the hydrogen atoms in this CH_2 -group are replaceable by metals. This is proved by the fact that diones of the composition $\text{RCOC}(\text{R})_2\text{COR}_1$ do not form metal compounds. Thus diones of the type $\text{RCOCH}_2\text{COR}_1$ have the character of very weak acids.

Pentan-2,4-dione, acetylacetone, $\text{CH}_3\text{COCH}_2\text{COCH}_3$, is obtained by the method of CLAISEN and WISLICENUS by the condensation of ethyl acetate with acetone. It is a colourless liquid with a pleasant smell, boiling at 127° and with a spec. grav. of 0.979 at 14° . It is split up into acetone and acetic acid by boiling with water. This is an example of a compound, which (because it contains a carbon atom attached to negative groups) is easily decomposed by water (compare 128, 129).

Acetylacetone gives salts with practically all metals. In the alkali salts the metal atom is ionogenically combined to the oxygen atom of the enol group. The alkali salts are unstable; the sodium salt is decomposed by water into acetone and sodium acetate.

In the salts of aluminium, copper and many other heavy metals, the metal atom is combined as a complex. These salts are readily soluble in non-polar solvents like chloroform or benzene but slightly soluble in water. They are dissociated to a slight extent only in the latter solvent. These salts are stable compounds; many of them can be distilled without decomposition; the vapour densities of the aluminium salt and the beryllium salt can be determined and from the results it is possible to derive the valency of these metals in the compounds $\text{Al}(\text{C}_5\text{H}_7\text{O}_2)_3$ and $\text{Be}(\text{C}_5\text{H}_7\text{O}_2)_2$.

These compounds are looked upon as internal complex salts in which the metal atom forms part of two (or more) heterocyclic six-rings (I):



A similar formula holds for the beryllium salt with a coordination number of 4.

With a complex beryllium compound from benzoylpyruvic acid $\text{C}_6\text{H}_5\text{COCH}_2\text{COCOOH}$, it has been shown that it is resolvable into optical antipodes. From this it follows that the oxygen atoms are arranged around the beryllium atom in the form of a tetrahedron in agreement with formula (II) (MILLS).

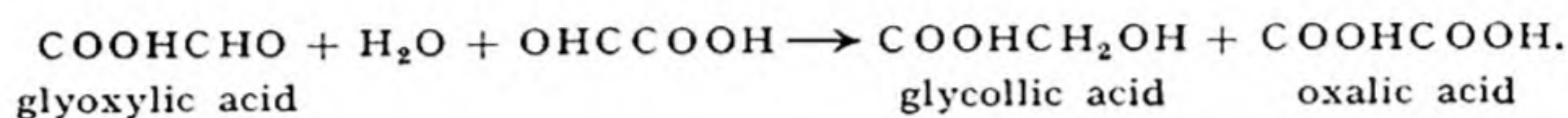
For similar complex compounds from amino-acids see 194 and from boric acid see 168.

1,4-Diones. Acetonylacetone or *hexan-2,5-dione* is a colourless liquid, b.p. 190° , spec. grav. 0.979 at 21° , with a pleasant smell. For its preparation see 148. Various compounds with closed chains of atoms may be obtained from 1,4-diketones; these will be discussed in 311, 312 and 313.

(ix) ALDEHYDIC AND KETONIC ACIDS

147. *Ethanal acid, glyoxylic acid*, $\text{COOHCHO} \cdot \text{H}_2\text{O}$, is the first member of the series of aldehydic acids. This acid occurs in unripe fruits. It is obtained by heating dibromoacetic acid, CHBr_2COOH , with water or by the electrolytic reduction of oxalic acid.

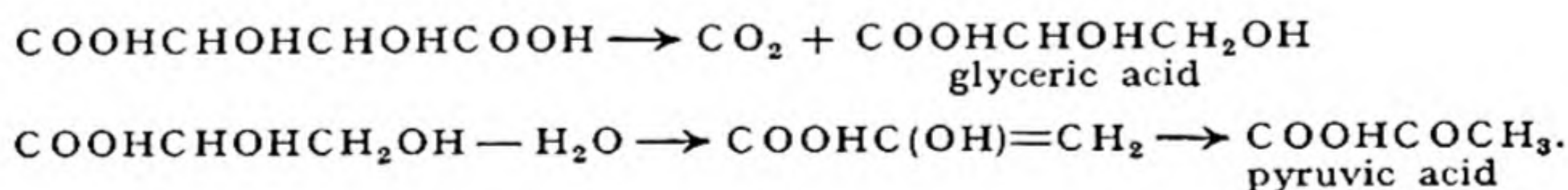
Glyoxylic acid possesses all the properties of the aldehydes (60) (reducing power, additive properties, ability to form oximes, etc.). On boiling with alkalis, it is converted into the salts of glycollic and oxalic acids, a transformation in accordance with the CANNIZZARO reaction (61) taking place:



Glyoxylic acid and its salts cannot be made to lose the molecule of water of crystallisation without decomposition, so that it is assumed that this water is chemically combined as in chloral hydrate (128) and mesoxalic acid (148). The formula is therefore $\text{CH}(\text{OH})_2\text{COOH}$. In these substances the group $-\text{CHO}$ or $>\text{CO}$ is under the influence of a negative group, viz. COOH and CCl_3 .

α -Ketopropionic acid, pyruvic acid, CH_3COCOOH , is the first member of the series of α -ketonic acids. The following is a general method for preparing α -keto-acids. The corresponding carbonitrile, which is converted into the α -keto-acid by hydrolysis, is produced from an acid chloride and potassium cyanide. Pyruvic acid can be produced by hydrolysis of the carbonitrile obtained from acetyl chloride and potassium cyanide according to the scheme: $\text{CH}_3\text{COCl} \rightarrow \text{CH}_3\text{COCN} \rightarrow \text{CH}_3\text{COCOOH}$.

Pyruvic acid is actually prepared from racemic acid or tartaric acid by distillation with acid potassium sulphate:



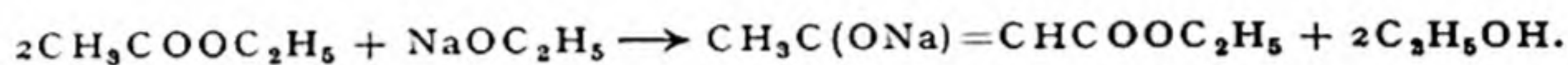
Since glyceric acid also forms pyruvic acid on heating with potassium bisulphate, it is probable, that in the above method of formation from racemic acid, glyceric acid is first produced by elimination of carbon dioxide, and this is then converted into pyruvic acid by loss of a molecule of water.

Pyruvic acid melts at 13° and boils at 165° ; the spec. grav. is 1.27 at 20° ; it is miscible in all proportions with water. It is much stronger than propionic acid for, $k = 0.0000134$ for propionic acid and 0.0056 for pyruvic acid. This is due to the effect of the negative carbonyl group adjacent to the carboxyl group.

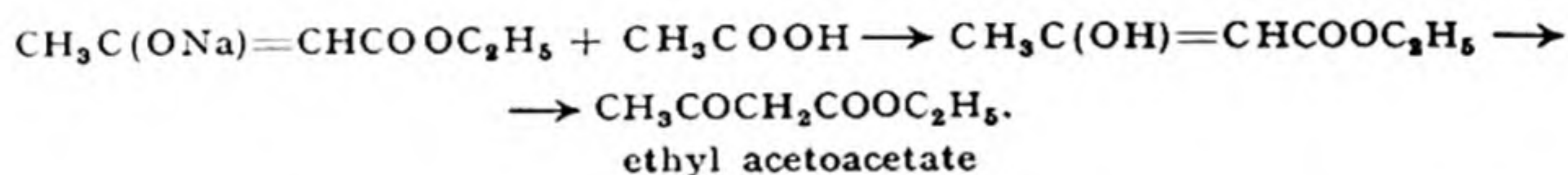
Pyruvic acid possesses all the properties of a ketone (64). It is easily recognized by the very sparingly soluble phenylhydrazone, which crystallises in beautiful long needles. The acid gives an intense orange-yellow colour with ferric salts. It is decomposed by warming with concentrated sulphuric acid, carbon monoxide is evolved. This is a general reaction for α -keto-acids.

Propanone carboxylic acid, β -keto-butyrac acid, *acetoacetic acid*, is a β -keto-acid $\text{CH}_3\text{COCH}_2\text{COOH}$, which is itself of very little importance. It occurs in the urine of sufferers from diabetes and is sometimes called *diacetic acid* in medicine.

148. Its ethyl ester, *ethyl acetoacetate*, which was synthesized by GEUTHER as early as 1865, is of very great importance however. The sodium compound of ethyl acetoacetate is prepared by the CLAISEN condensation (146) by treating ethyl acetate with sodium ethylate; for this purpose a preparation of ethyl acetate is used in which a little ethanol is present; when this is warmed with one equivalent of sodium, it produces sodium alcoholate which then acts as a condensing agent:



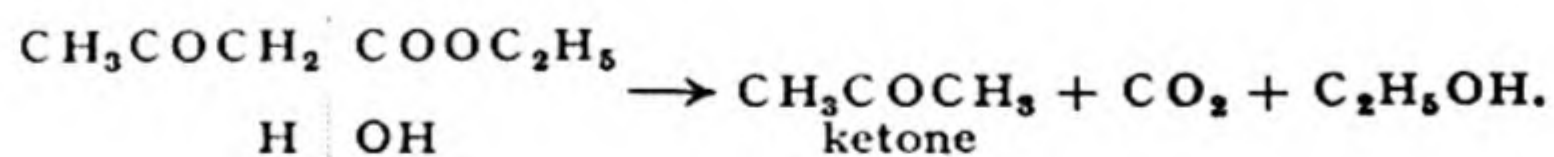
On treating the mixture with acetic acid, ethyl acetoacetate is produced:



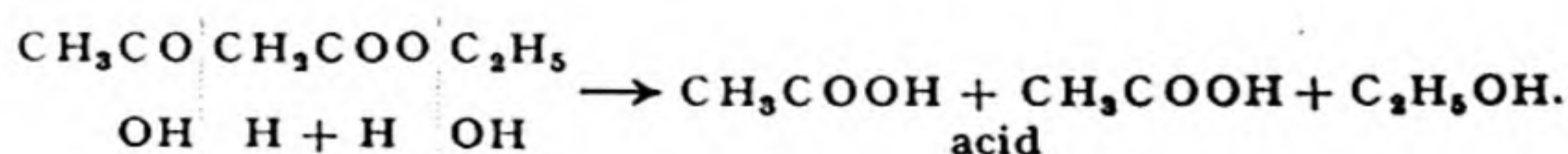
This is again an example where the grouping $-\text{C}(\text{OH})=\text{CH}-$ passes over into $-\text{CO}-\text{CH}_2-$. (146).

Ethyl acetoacetate is a colourless liquid with a pleasant smell, b.p. 181° , spec. grav. 1.030 at 15° . It is slightly soluble in water and gives a bluish red colour with a solution of ferric chloride.

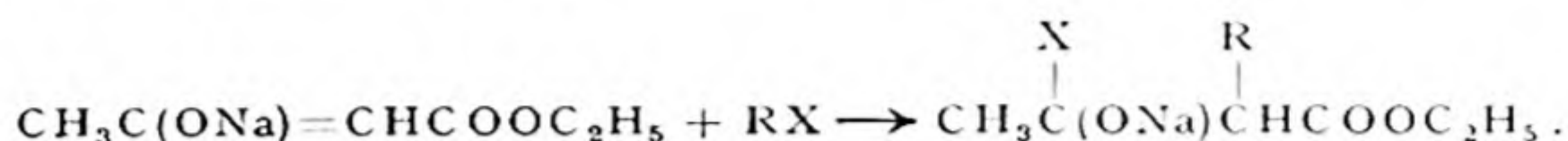
When ethyl acetoacetate is heated with dilute sulphuric acid or with a dilute solution of alkali in water, acetone, carbon dioxide and alcohol are produced. This is called *ketone fission*:



When, however, ethyl acetoacetate is warmed with very concentrated alcoholic caustic alkali, acetic acid and ethyl alcohol are produced. This is known as *acid fission*:

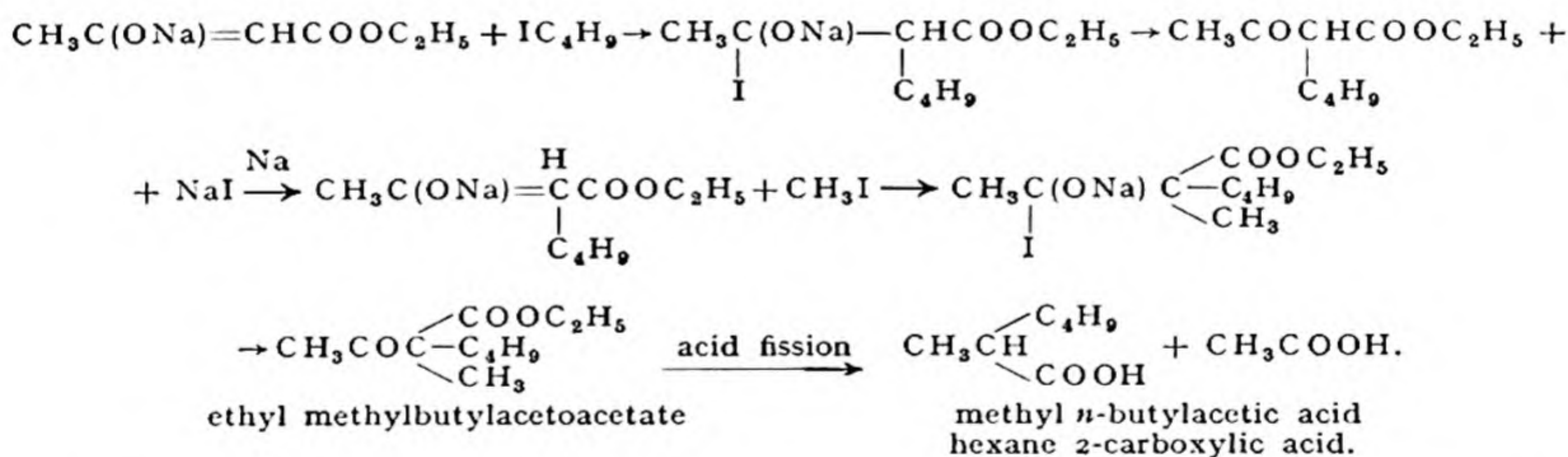


The hydrogen atoms in the CH_2 group in ethyl acetoacetate are replaceable by various groups. Alkyl groups can be introduced by the action of alkyl halides on the sodium compound of ethyl acetoacetate:

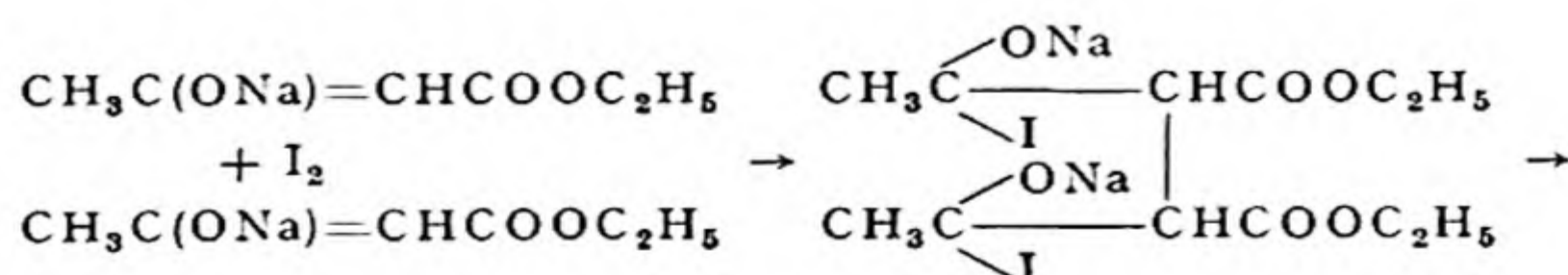


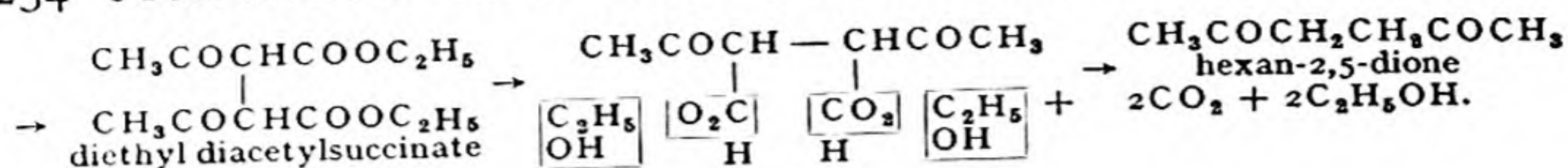
This addition product splits off NaX and a homologue of ethyl acetoacetate, viz. $\text{CH}_3\text{COCHRCOOC}_2\text{H}_5$, is produced. The remaining hydrogen atom in the group $-\text{CHR}$ may again be substituted by an alkyl residue in the same way, giving compounds of the type $\text{CH}_3\text{COC}(\text{R}_1\text{R}_2)\text{COOC}_2\text{H}_5$. When the compounds so obtained are subjected to a ketone fission, homologues of acetone are produced, while application of the acid fission, produces homologues of acetic acid. Thus ethyl acetoacetate may be used as the starting material for the synthesis of many ketones and alkane carboxylic acids.

1. Preparation of *hexane 2-carboxylic acid* (see also 161). By the action of *n*-butyl iodide on the sodium derivative of ethyl acetoacetate, ethyl butylacetoacetate is produced, from which ethyl methylbutylacetoacetate is obtained by subsequent interaction with methyl iodide. Hexane 2-carboxylic acid is then produced from this compound by acid fission:



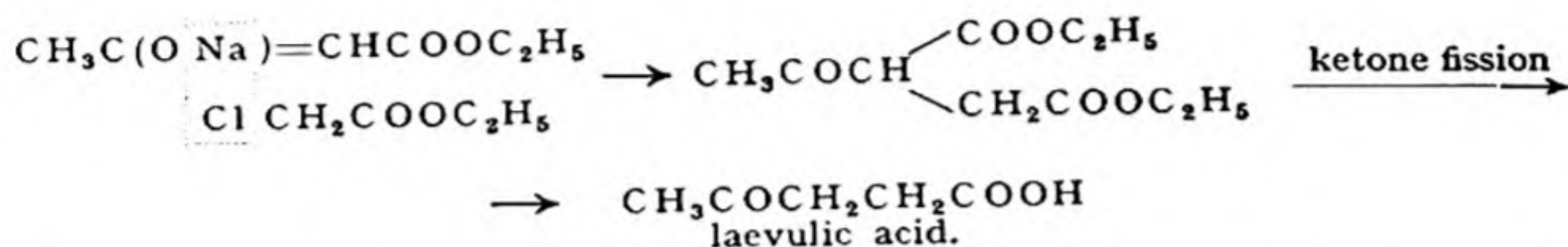
2. Preparation of *1,4-diones (diketones)*. By the action of iodine on the sodium derivative of ethyl acetoacetate, two molecules combine and by splitting off two molecules of sodium iodide an ester, diethyl hexan-2,5-dione 3,4-dicarboxylate, diethyl diacetylsuccinate, is produced, which on boiling with 20 % caustic potash solution, takes up water (ketone fission), easily splits off carbon dioxide and alcohol and passes over into hexan-2,5-dione or acetonylacetone (146):





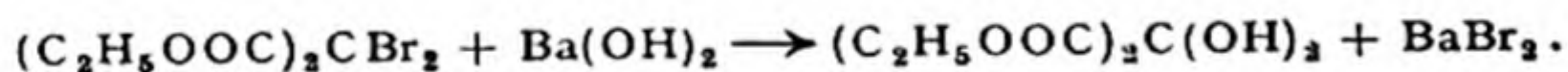
The structure of the 1,4-dione follows from this synthesis.

Laevulic acid, *butan-3-one 1-carboxylic acid*, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$, is the simplest γ -keto-acid. γ -Keto-acids are prepared by the action of the sodium derivative of ethyl acetoacetate on esters of 1-halogeno-fatty acids, which produces compounds giving γ -keto-acids by ketone fission. An ester of monochloroacetic acid is used for the preparation of laevulic acid:



Laevulic acid is also prepared from hexoses, especially from fructose (laevulose) (163) by treatment with concentrated hydrochloric acid. In this process hydroxymethylfurfuraldehyde is produced as an intermediate product. Laevulic acid melts at 37.2° and boils at 250° . It gives a phenylhydrazone and an oxime and can be reduced by sodium amalgam to a 3-hydroxy-acid. With bromine it gives *dibromolaevulic acid*, m.p. 115° . The acid can be identified by this means and also as the silver salt.

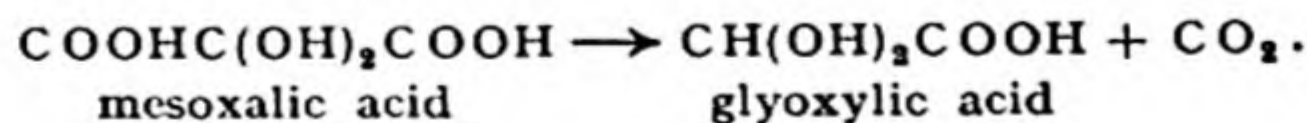
Mesoxalic acid, *ketomethane dicarboxylic acid*, $\text{C}_3\text{H}_2\text{O}_5 \cdot \text{H}_2\text{O}$, is a *dibasic keto-acid*. It is a fission product of uric acid (346); the diethyl ester is obtained by boiling diethyl dibromomalonate with baryta water:



Mesoxalic acid melts at 121° and like glyoxylic acid (147) contains a molecule of water. An ester of the anhydrous acid is known; this has a greenish yellow colour which must be ascribed to the direct bonding of three CO-groups, $\text{C}_2\text{H}_5\text{O}-\text{C}-\text{C}-\text{C}-\text{OC}_2\text{H}_5$ (145).

$$\begin{array}{c}
 \text{O} \quad \text{O} \quad \text{O} \\
 || \quad || \quad || \\
 \text{C} - \text{C} - \text{C}
 \end{array}$$

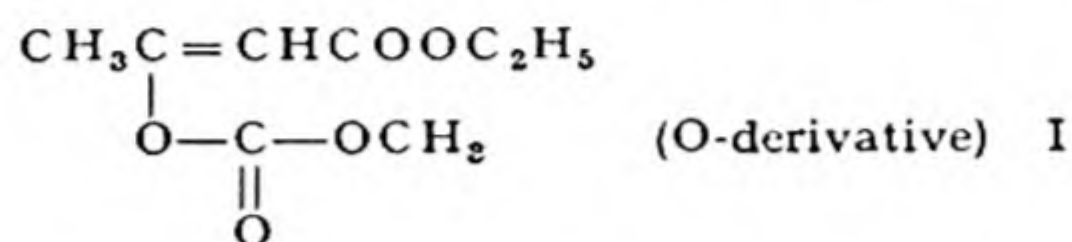
The ester easily adds on a molecule of water and the resultant hydrate is colourless. Mesoxalic acid possesses most of the properties of the ketones (64). On boiling with water it loses carbon dioxide and is converted into glyoxylic acid:



This fission takes place much more easily than with malonic acid (123), because the carbon atom is loaded with four negative groups.

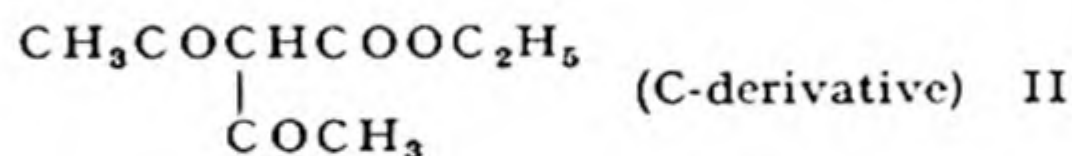
Tautomerism

149. Ethyl acetoacetate can combine with sodium bisulphite or hydrogen cyanide by addition. These are properties of a compound containing a ketone grouping. When ethyl acetoacetate is treated with acetyl chloride in the presence of pyridine which fixes the hydrogen chloride as it is formed, an acetate, the O-derivative, is produced to which the structure:



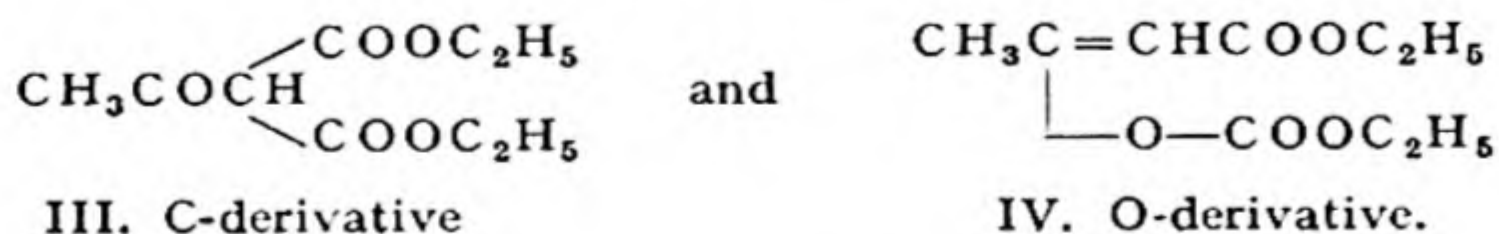
must be ascribed, since this compound adds on two atoms of bromine at low temperatures and therefore contains a carbon double bond. By the action of alkali at ordinary temperatures, the substance is split up into sodium acetate and ethyl acetoacetate. Thus, in the formation of this acetate, ethyl acetoacetate reacts as if it were a compound with an OH-group with the structural formula $\text{CH}_3\text{C}(\text{OH})=\text{CHCOOC}_2\text{H}_5$.

If, however, acetyl chloride is allowed to react on the sodium derivative of ethyl acetoacetate, the main product of the reaction, along with a small amount of I, is an isomeric compound, the C-derivative, of the structure:



for this compound no longer adds on bromine and on heating with water at 150° is split up into carbon dioxide, ethyl alcohol and acetylacetone, $\text{CH}_3\text{COCH}_2\text{COCH}_3$. From the formation of the C-derivative II it might be concluded that the sodium compound from ethyl acetoacetate has the structure $\text{CH}_3\text{COCHNaCOOC}_2\text{H}_5$.

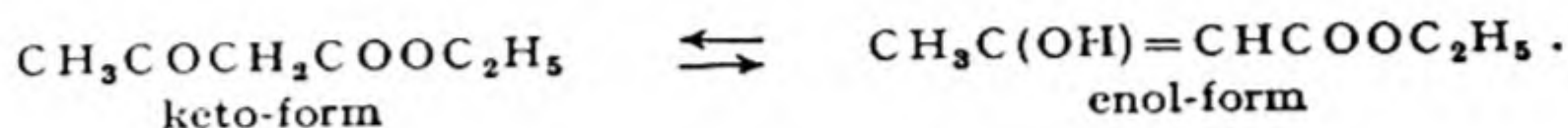
Another example, in which the sodium derivative of ethyl acetoacetate can react in two different ways is to be found in the action of ethyl chloro-carbonate, $\text{ClCOOC}_2\text{H}_5$ (150), in which two compounds are produced:



The presence of a carbon double bond in IV is demonstrated by the addition of bromine.

In 148 it was mentioned that compounds having the structure $\text{CH}_3\text{COCHRCOOC}_2\text{H}_5$, are produced by the interaction of alkyl halides and the sodium derivative of ethyl acetoacetate, as is apparent from the course

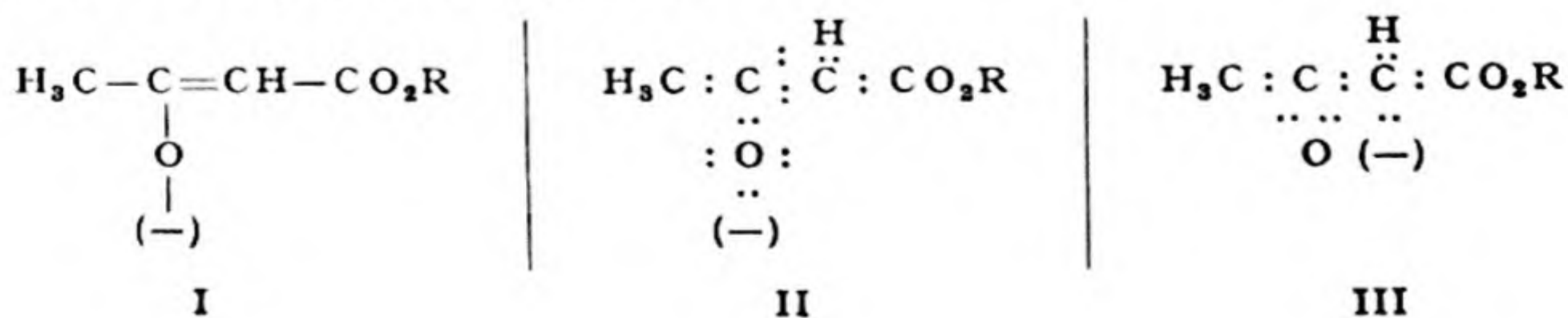
of both acid and ketone fission. On this account, the sodium derivative of ethyl acetoacetate used to be formulated as $\text{CH}_3\text{COCHNaCOOC}_2\text{H}_5$. Later on, however, it appeared that this sodium compound must be regarded as $\text{CH}_3\text{C(ONa)=CHCOOC}_2\text{H}_5$, so that the reaction with alkyl halides must be formulated in the way given in 148. For a long time therefore, there was some uncertainty as to which structure should be ascribed to ethyl acetoacetate until it was shown, that in the liquid state or when dissolved in a solvent, this substance consisted of a mixture of two isomeric compounds, which are rapidly and reversibly interconvertible one into the other:



The two isomeric forms were isolated as follows by KNORR (1911). On cooling a concentrated solution of ethyl acetoacetate in ethanol to very low temperatures, a substance crystallises out, which melts at -39° ; this substance gives no colour reaction with ferric chloride and the refractive index is 1.4225 at 10° . When the equivalent quantity of dry gaseous hydrogen chloride is led into a suspension of the sodium derivative of ethyl acetoacetate in light petroleum at low temperatures, and the precipitated sodium chloride is filtered off and the light petroleum evaporated in a vacuum at a low temperature, a liquid remains behind, which is still a liquid at -78° and gives a violet colour at this temperature with ferric chloride and has a refractive index of 1.4480 at 10° . This isomer must be the enol-form, since the refractive index of a substance with a —C=C— bond has a higher value than that of an isomer with a C=O bond. From this experiment it is apparent also, that the *sodium derivative* of ethyl acetoacetate has the enol-structure.

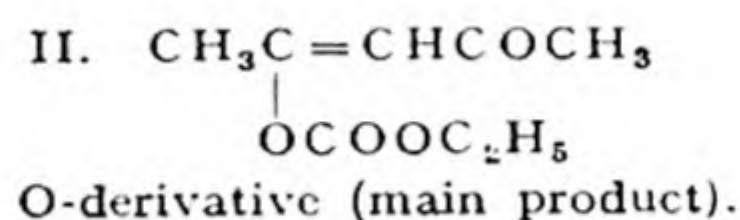
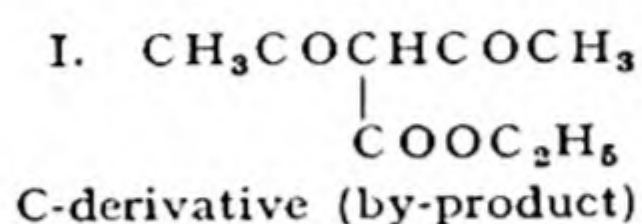
The two isomerides remain unchanged at very low temperatures, but at 20° they change rapidly until a state of equilibrium is reached. The particular kind of isomerism in which two isomeric forms rapidly and reversibly pass into one another, is called *tautomerism* or *desmotropism*. In this case, in which substances containing an enol-group and a keto-group change over one into the other, it is known as *keto-enol-tautomerism*.

The sodium derivative of acetoacetic ester is a salt of the enol-form, which is to be regarded as a weak acid. It is possible to envisage for the anion of this salt—the enolate ion (I)—two electronic structures, which differ only in the arrangement of the valency electrons (II and III)

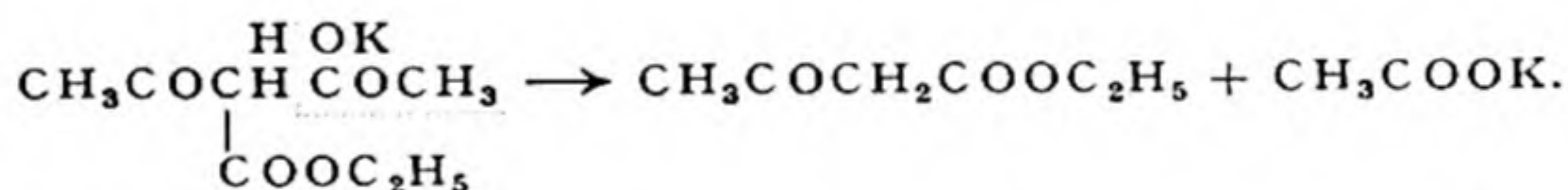


The enolate ion is to be considered as a mesomeric form (214), it is probable that the reaction between the sodium compound of acetoacetic ester and an alkyl halide proceeds by an ionic mechanism, i.e. that the alkyl halide is to a small extent split into ions $C_2H_5^+$ and X^- . In the formation of an O-derivative, the enolate ion reacts according to the valency structure (II); in the formation of a C-derivative, according to the valency structure (III).

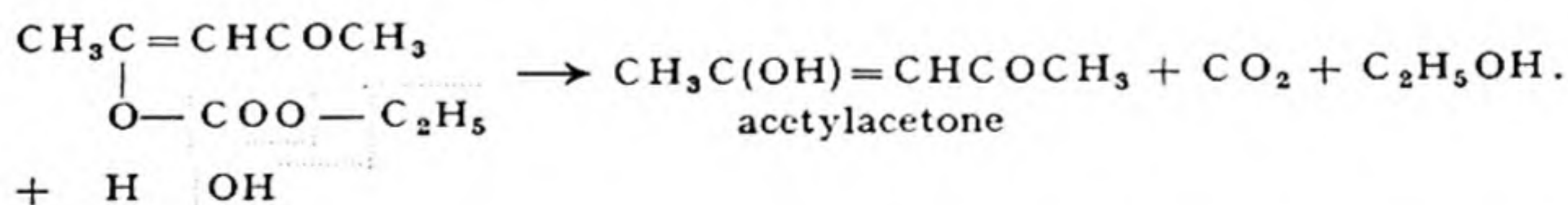
This phenomenon is not restricted to ethyl acetoacetate but is of general occurrence in esters of other 2-keto-acids and in 1,3-diketones; the condition for this tautomerism is therefore that a CH_2 -group is situated between two $>C=O$ -groups, between a $>C=O$ -group and a $O=C<-OC_2H_5$ -group, or between two $O=C<-OC_2H_5$ -groups. C-derivatives and O-derivatives can be formed also from 1,3-diketones. Thus by the action of ethyl chlorocarbonate on the sodium derivative of acetylacetone, two compounds are produced:



The structure of compound I follows from its degradation into potassium acetate and ethyl acetoacetate by warming with one equivalent of caustic potash:



Compound II is split up into acetylacetone, alcohol and carbon dioxide by dilute alkali at ordinary temperatures:



1,3-Diketones and 2-keto-esters all give a violet colouration in solution with ferric chloride. It has already been mentioned that this reaction is due to the enol-form, and hence to the grouping $-C(OH)=CH-$. (Compare the reaction of ferric chloride with phenols 229). Derivatives of these enol-forms, O-derivatives, which can be isolated more easily than the free enol-forms, immediately add on bromine. K. H. MEYER has shown that 2-keto-esters and 1,3-diketones also add on bromine in alcoholic solution, which must be due to the presence of these substances in the enol form. He was able, on this reaction, to base a method for the determination of the enol-content by measuring how much of a solution of bromine in alcohol was immediately decolourised at low temperatures. In this way, it was found that the enol-content varied very considerably in different solvents; the figures for the

state of equilibrium for ethyl acetoacetate and acetylacetone are given in Table 35.

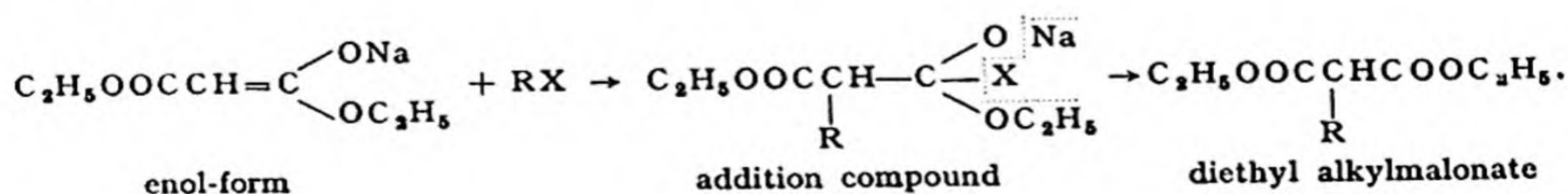
TABLE 35
PER CENT. ENOLISATION IN VARIOUS SOLVENTS

Solvent	Ethyl acetoacetate % enol	Acetylacetone % enol
None	7.4	76
Water (0°)	0.4	19
Glacial acetic acid	5.7	74
Methanol (0°)	6.9	72
Ethanol (0°)	12.7	84
Chloroform (20°)	8.2	79
Benzene (20°)	18.0	85
Hexane (20°)	48.0	92

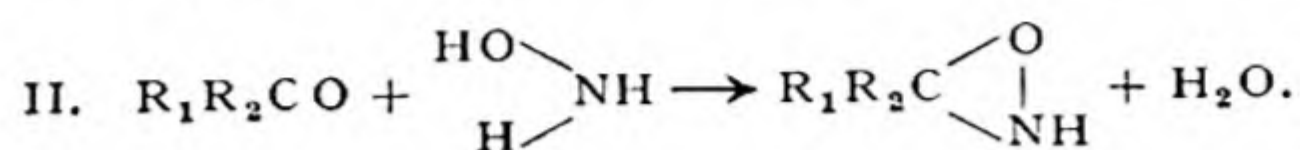
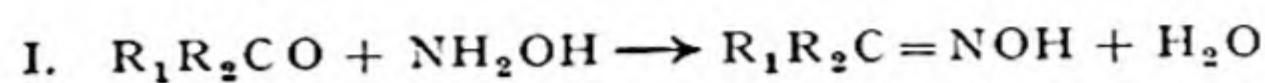
It is seen that the degree to which a substance is enolised, depends on the constitution, (acetylacetone is much more strongly enolised than ethyl acetoacetate) and in addition is strongly influenced by the solvent. Hexane and benzene are "enolising" solvents, water is a "ketonising" solvent. The effect of the solvent on the keto-enol equilibrium must be ascribed to the difference in the heat of mixing of the keto- and the enol-forms with the solvent. The temperature has little effect on the equilibrium. In general, this is displaced a little to the keto-side by increase in temperature.

Substances which show keto-enol tautomerism are soluble in dilute caustic soda, since the enol-form dissolves with the formation of the sodium enolate (compare the solubility of phenol in caustic soda). Hence, when a 1,3-diketone is dissolved in dilute caustic alkali, the keto-form is converted into the enol-form.

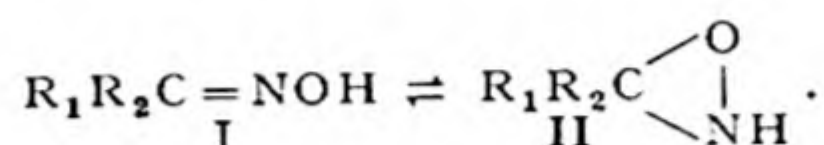
In ethyl malonate, a CH_2 -group is situated between two $-\text{CO}-\text{OC}_2\text{H}_5$ -groups. A hydrogen atom of this CH_2 -group can be replaced by sodium. It is obvious to assume the conversion into an enol-form in this case also. Indeed by the addition of bromine it is possible to show that sodium ethyl malonate has an enol-structure. The action of alkyl halides (RX) on sodium ethyl malonate must be represented as follows:



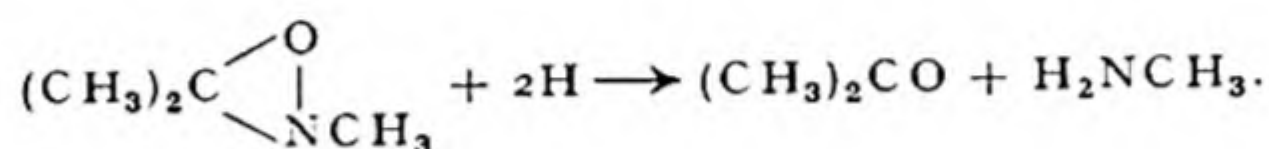
Tautomerism of oximes. Oximes are produced by the action of hydroxylamine on aldehydes and ketones (59). This reaction can be represented in two ways:



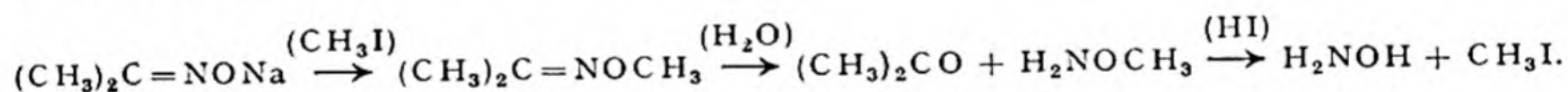
Now it appears that oximes can react as though they possess both the structures (I) and (II), so that they are tautomeric:



When propanone oxime is treated with methyl iodide, the methyl group combines with the nitrogen atom, for methylamine and acetone are produced on reduction:



When sodium methylate is added to the mixture of propanone oxime and methyl iodide, the sodium derivative of the ketoxime is first of all formed from which the action of methyl iodide produces a compound giving acetone and methoxyamine on hydrolysis with hydrochloric acid. On heating with hydriodic acid, the methoxyamine is split up into methyl iodide and hydroxylamine, by which it is proved that methyl is attached to oxygen in this compound:

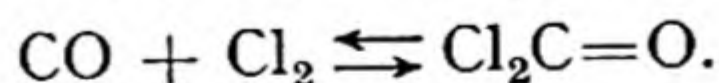


(x) DERIVATIVES OF CARBONIC ACID AND RELATED COMPOUNDS

(a) *Derivatives of carbonic acid*

150. *Carbonic acid* H_2CO_3 or $CO(OH)_2$, which may also be considered as the hypothetical hydroxyformic acid, is unknown. It is assumed that this dibasic acid occurs in small quantities in an aqueous solution of carbon dioxide. A number of organic derivatives of this hypothetical acid are known, however.

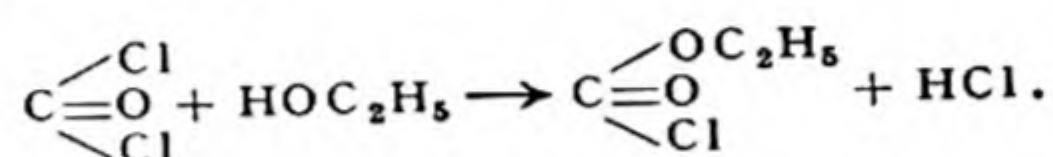
Carbonyl chloride, carbon oxychloride or *phosgene*, $Cl_2C=O$, is produced by the addition of chlorine to carbon monoxide at a high temperature. At 503° the equilibrium lies at about 67 % of the dissociation products:



Phosgene is dissociated by ultra-violet light (especially of very short wavelength) into carbon monoxide and chlorine, a photochemical state of equilibrium being produced.

The name phosgene was given to this substance by J. DAVY (1811) because he was of the opinion that the combination of the two gases could take place only in sunlight; later on it was found that this is not the case. It is prepared on a commercial scale by passing a mixture of carbon monoxide and chlorine over animal charcoal at 200°. Phosgene gas has a penetrating odour and is very poisonous. The boiling point lies at + 8.2°; the setting point at -118°; the spec. grav. is 1.432 at 0°. It is readily soluble in benzene; it is used for synthetic purposes, for example, in the dyestuffs industry.

Carbonyl chloride can undergo all the reactions which are characteristic for acid chlorides. It must be considered therefore, as the chloride of carbonic acid. It reacts with water with the formation of hydrochloric acid and carbonic acid. With alcohol at ordinary temperature, *ethyl chlorocarbonate* is first of all produced:



By prolonged action of alcohol or by the action of sodium alcoholate, *diethyl carbonate* $\text{CO}(\text{OC}_2\text{H}_5)_2$ is produced. By the action of ammonia the two chlorine atoms are replaced by amino-groups; *urea* $\text{CO}(\text{NH}_2)_2$ is produced.

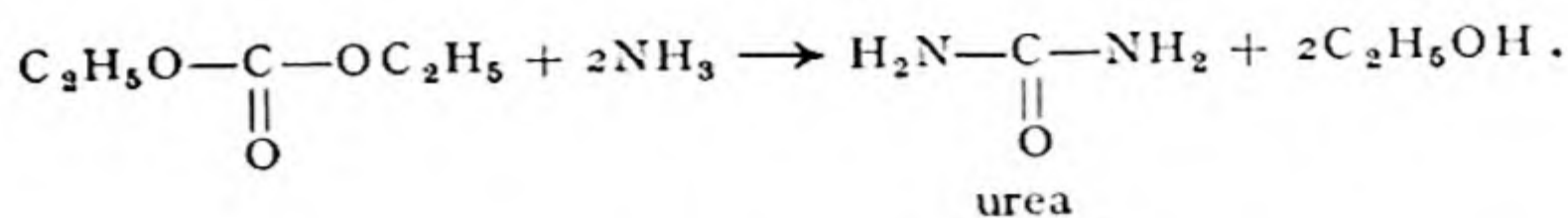
The chlorocarbonates are colourless liquids with a powerful unpleasant odour, which distil without decomposition. They may be used for introducing the carbethoxyl group, COOC_2H_5 (149), for example, into various kinds of compounds.

The esters of carbonic acid also are liquids; they possess an ethereal odour. They are insoluble in water and easily hydrolysed.

151. *Urea* or *carbamide*, $\text{CO}(\text{NH}_2)_2$, melts at 132° and is readily soluble in water. It occurs to the extent of about 2 % in urine (Greek ούρον); an adult eliminates about 30 g. of urea per day. This substance is produced in the body by the degradation of proteins and besides being found in the urine of mammals, amphibia and fishes, it occurs also in the vegetable kingdom, e.g. in moulds.

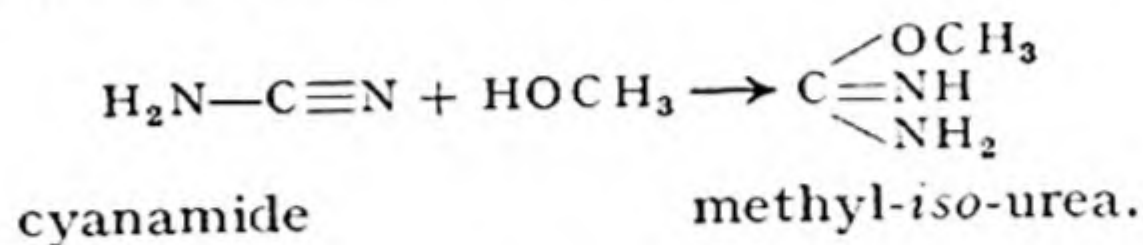
BOERHAAVE had already described the isolation of urea in 1732 (see 1). It was isolated from urine by ROUELLE in 1773 and was investigated later by FOURCROY and VAUQUELLIN and by WILLIAM PROUST, who determined the composition.

The structure of urea follows from its formation from carbonyl chloride or from esters of carbonic acid (150); the substance is to be regarded as the di-amide of carbonic acid:

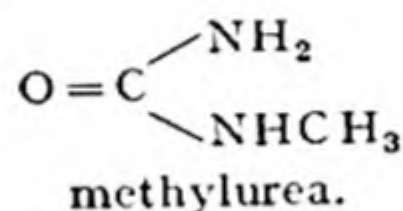


Like amines, urea combines with acids to form salts. The *nitrate*, $\text{CO}(\text{NH}_2)_2 \cdot \text{HNO}_3$ and the *oxalate*, $2\text{CO}(\text{NH}_2)_2 \cdot \text{C}_2\text{H}_2\text{O}_4$, are sparingly soluble in solutions of the corresponding acids. Since urea combines with only one equivalent of acid, it may be supposed that it has the structure $\text{C} \begin{smallmatrix} \nearrow \text{NH} \\ \text{---} \text{OH} \\ \searrow \text{NH}_2 \end{smallmatrix}$ in these salts.

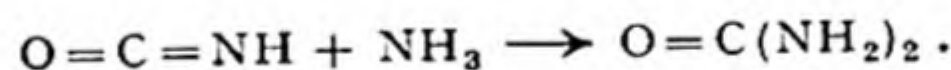
An ether of this *iso*-urea is produced by the addition of methyl alcohol to cyanamide (155) under the action of hydrochloric acid:



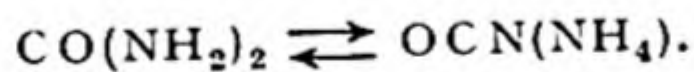
On heating with hydrochloric acid, methyl chloride is produced from methyl-*iso*-urea. The methyl group is not attached to nitrogen therefore, for, under the same conditions, methylurea splits off methylamine:



Urea is produced when an aqueous solution of ammonium cyanate is evaporated. In this way WÖHLER obtained urea in 1828 by evaporating a solution of potassium cyanate and ammonium sulphate (1). This reaction is very useful as a preparative method for urea. It is assumed in this case that a molecule of ammonia is added to *isocyanic acid* (155):

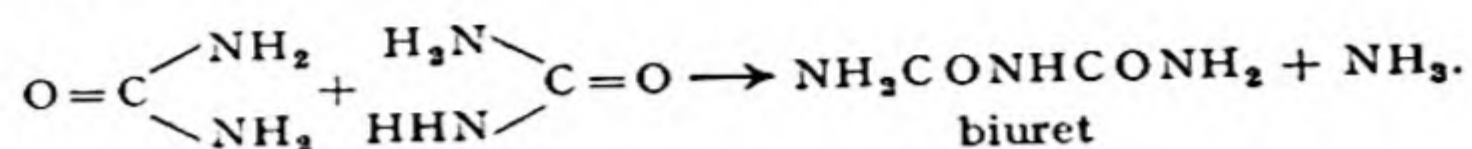


An equilibrium is set up in this reaction, for silver nitrate gives a precipitate of silver cyanate when added to a solution of urea in boiling water:

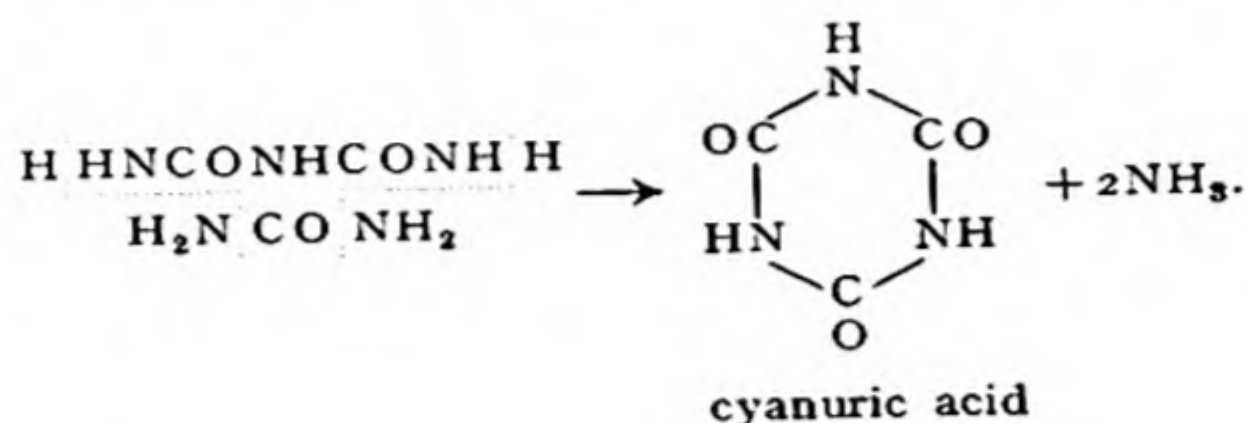


This equilibrium is situated well over on the urea side, however, since only a small proportion of cyanate is present (WALKER and HAMBLY). The position of the equilibrium is only slightly dependent on the temperature; from this it follows that the conversion of either of the products into the other is associated with a small heat effect only.

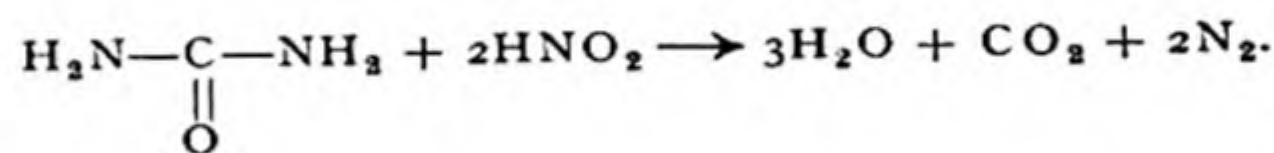
On heating urea, two molecules combine with the elimination of ammonia to form *biuret*, a substance melting at 193° , which is sparingly soluble in cold water:



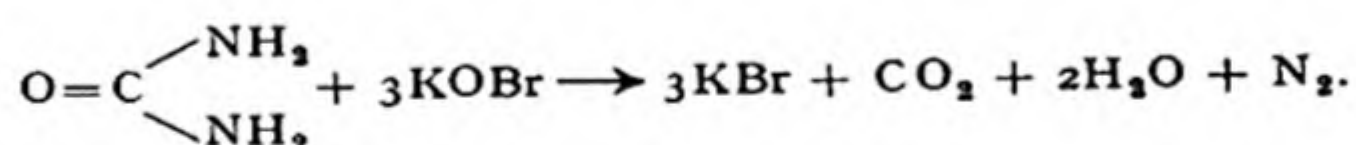
This substance gives a reddish violet colour with copper sulphate and caustic alkali (*biuret reaction*). On heating further, biuret combines with another molecule of urea and cyanuric acid (156) is produced:



Urea, as an acid amide, is decomposed into carbonic acid and ammonia by heating with acids or bases. This hydrolytic fission takes place at ordinary temperatures under the influence of an enzyme *urease* (208), which occurs, for example, in soya-beans and in some micro-organisms. By the action of nitrous acid, urea is decomposed into carbon dioxide, water and nitrogen:



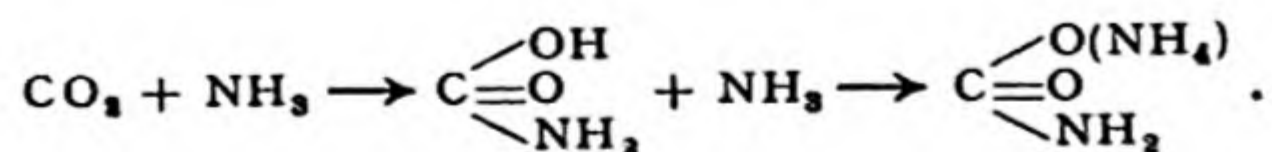
Urea is split up into carbon dioxide, water and nitrogen, also by the action of bromine and caustic alkali (hypobromite). A method for determining the urea content of urine in which the volume of nitrogen is measured, is based on this reaction:



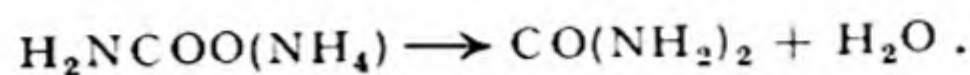
Urea is manufactured on a large scale; it is used for example, as a constituent of artificial fertilisers, as the starting material for certain synthetic resins and for some pharmaceutical products.

(b) Derivatives of carbamic acid

152. Carbamic acid, the half-amide of carbonic acid, is unknown. The *ammonium salt* is produced by the combination of dry carbon dioxide and ammonia:

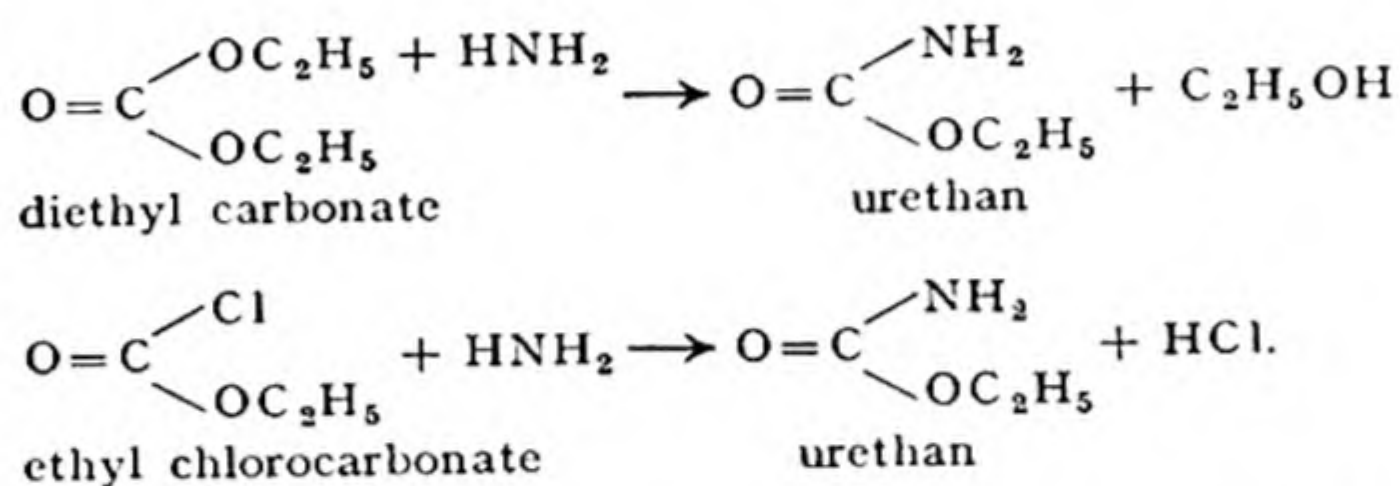


This reaction is of importance for the technical synthesis of urea, which is produced by heating ammonium carbamate to 130-140° under pressure:

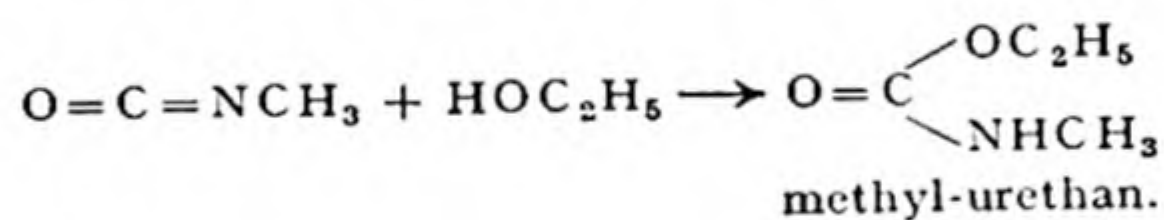


Calcium carbamate, $\text{Ca}(\text{OCONH}_2)_2$, is produced by passing carbon dioxide into an ammoniacal solution of calcium chloride. This compound is soluble in water. On warming aqueous solutions of the salts of carbamic acid, the latter are converted into carbonates and ammonia, a molecule of water being taken up in the process.

The *esters of carbamic acid* are called *urethans*. They are produced from esters of carbonic acid or from the corresponding chlorocarbonates and ammonia or an amine:



Urethans are also produced by the addition of alcohols to *isocyanates*:



This reaction is important for demonstrating the presence of alcoholic hydroxyl groups.

Most urethans are well defined, crystalline compounds, which can be distilled without decomposition. They are split up into carbon dioxide, ammonia and alcohol by boiling with bases.

Ordinary urethan $\text{NH}_2\text{COOC}_2\text{H}_5$, melts at 51° and is readily soluble in water.

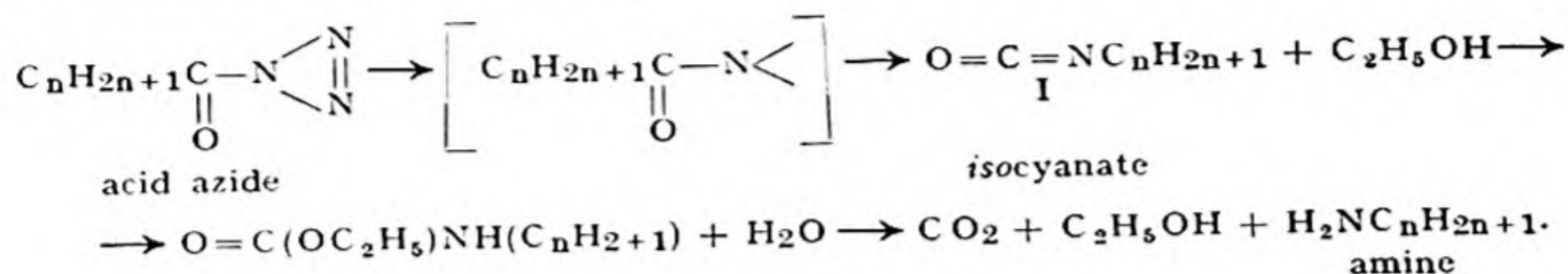
Some urethans, such as $\text{H}_2\text{NCO}[\text{OC}(\text{CH}_3)_2\text{C}_2\text{H}_5]$, *Aponal*, are used as sedatives or hypnotics. *Neuronal* is a brominated acid amide $(\text{C}_2\text{H}_5)_2\text{CBrCONH}_2$, while *Adalin*, $(\text{C}_2\text{H}_5)_2\text{CBrCONHCONH}_2$ and *Bromural* $(\text{CH}_3)_2\text{CHCHBrCONHCONH}_2$, are *ureides*; ureides are derivatives of urea in which a hydrogen atom of one of the amino groups is replaced by an acid residue (cyclic ureides are discussed in 344).

Nitramines. When a urethan is treated with cold absolute nitric acid a nitrourethan, e.g. $\text{C}_2\text{H}_5\text{OCONHNO}_2$, is produced, which may be regarded as a nitramine, i.e. a compound of the general formula $\text{R}_1\text{R}_2\text{NNO}_2$, (FRANCHIMONT).

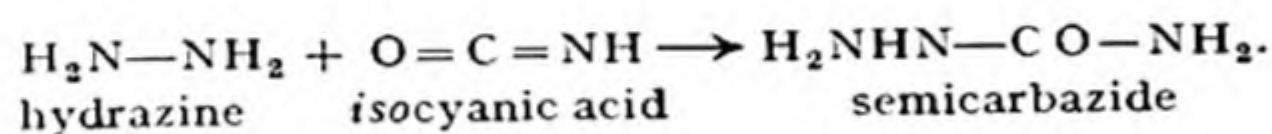
Besides the mono-alkylurethans other substituted acid amides RCONHR_1 , can be nitrated. In this way a compound $\text{RCONR}_1\text{NO}_2$ is produced from which the acid residue can be removed by ammonia with the formation of a nitramine R_1NHNO_2 .

By careful reduction, a substituted hydrazine can be obtained from this compound. This reaction establishes the structure of these compounds.

Urethans are formed as intermediate products in the conversion of acid azides into primary amines by the CURTIUS reaction (see 178). In this reaction an acid azide is warmed with alcohol when a molecule of nitrogen is eliminated; an unstable radical is formed which isomerises into an *isocyanate*. The latter then combines with the alcohol with the formation of a urethan, from which a primary amine is obtained by hydrolysis with acids or alkalis:

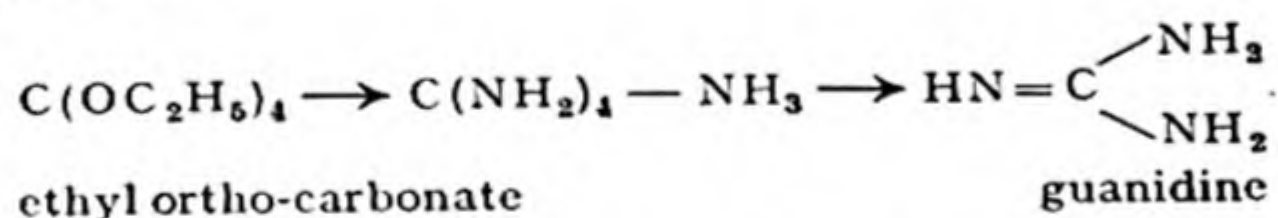


Semicarbazide, $\text{H}_2\text{NCONHNH}_2$, may be considered as the hydrazide of carbamic acid; it melts at 96° , reacts neutral in aqueous solution and gives salts with one equivalent of acid. Semicarbazide is prepared by the action of a solution of hydrazine sulphate on potassium cyanate in water, when addition of hydrazine to *isocyanic acid* (155) must be assumed to take place:

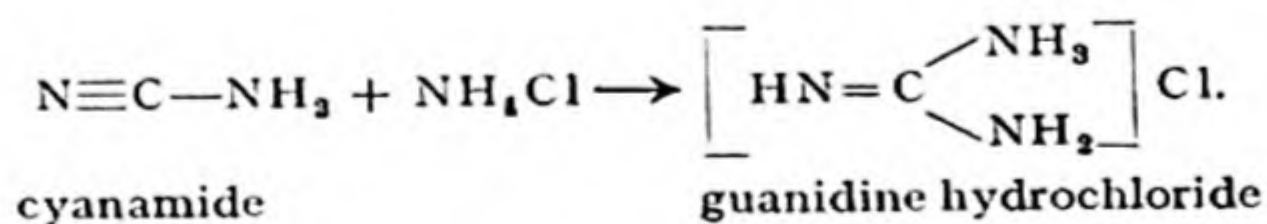


The formation of semicarbazones from semicarbazide and aldehyde or ketones has already been discussed in 59.

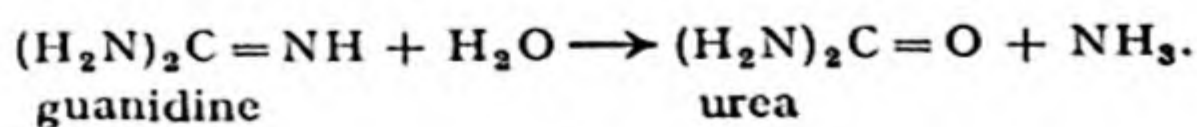
153. *Guanidine* CH_5N_3 is produced by the action of ammonia on ortho-carbonates. It may be supposed that the alkoxy groups are replaced by four amino groups and that the compound so produced immediately loses a molecule of ammonia:



The above structure is confirmed by the preparation of guanidine from cyanamide (155) and an alcoholic solution of ammonium chloride at a high temperature:



Guanidine is split up into ammonia and urea by treatment with baryta water or by the action of putrifying bacteria:



Guanidine is a crystalline substance, which takes up carbon dioxide and water from the atmosphere and is readily soluble in water and in alcohol. It is a strong base, which differs only slightly in degree of ionisation from the caustic alkalis. When guanidine is compared with urea, which reacts neutral, it is seen that the basic properties greatly increase when the oxygen atom in the carbonyl group is replaced by the imino group. Guanidine was first obtained by STRECKER from *guanine* (348), a substance occurring in guano.

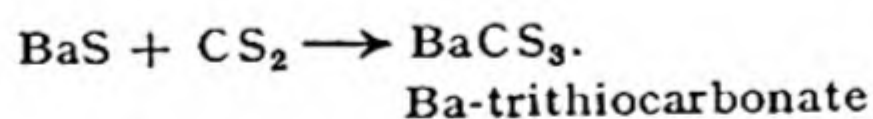
(c) *Carbon disulphide and its derivatives*

154. *Carbon disulphide*, CS_2 , is prepared on a technical scale by passing sulphur vapour over wood charcoal at 900° . This is a direct synthesis from the elements. Carbon disulphide is an endothermic substance, the heat of formation being -19 kcal. The crude product has an extremely unpleasant odour, which is removed, however, by distillation over any kind of fat; a colourless, highly refracting, ethereal smelling liquid with b.p. 46.2° and f.p. -111.6° , is then obtained. It is insoluble in water, poisonous and extremely inflammable and has a spec. grav. of 1.262 at 20° . It is an excellent solvent for fats and oils and finds application in the extraction of these substances from seeds. Carbon disulphide is used in large amounts in the manufacture of rayon by the viscose process (191). It is also used in the vulcanisation of rubber.

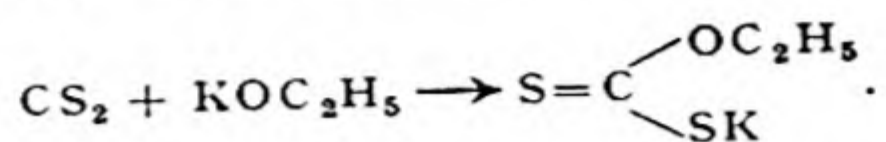
Carbon disulphide is only slightly attacked by chlorine or bromine at ordinary temperatures; if a halogen carrier is present, however, tetra-chloro- or tetra-bromo-methane is eventually produced.

Carbon disulphide gives an addition product, $\text{P}(\text{C}_2\text{H}_5)_3\text{CS}_2$, obtained in red crystals melting at 122° , with an ethereal solution of triethylphosphine (cf. 51). Small quantities of carbon disulphide can be detected in this way.

Trithiocarbonates are produced by the addition of alkali sulphides or alkaline earth sulphides to carbon disulphide. These are salts of *trithiocarbonic acid*:



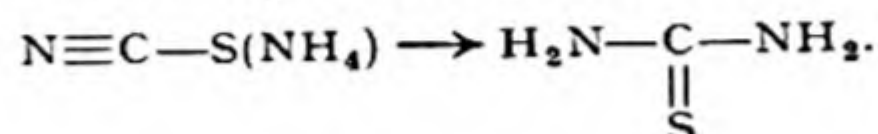
The barium salt is yellow and sparingly soluble in water. Trithiocarbonic acid, H_2CS_3 , can be obtained from the salts by the action of dilute acids, as a red oil which easily decomposes. The potassium salt is used for killing the vine pest (*phylloxera*). When carbon disulphide is shaken with a solution of potassium hydroxide in absolute alcohol the potassium salt of *xanthic acid* separates in glittering yellow needles:



Free xanthic acid, $\text{HSCSOC}_2\text{H}_5$, is a very unstable liquid, which after a short time begins to warm up spontaneously and finally decomposes violently into alcohol and carbon disulphide. This decomposition is a case of autocatalysis, since the liberated alcohol accelerates the reaction.

Xanthic acid owes its name to the fact that with copper sulphate a black-brown precipitate of cupric xanthate is produced, which very rapidly passes over into the corresponding cuprous salt which is yellow ($\xi\alpha\nu\delta\omicron\varsigma$ = yellow).

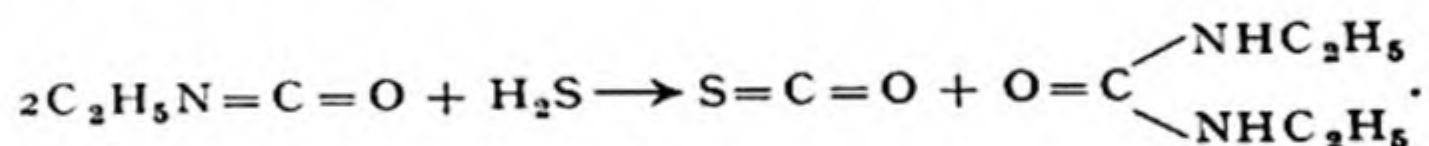
Thiourea, $(\text{H}_2\text{N})_2\text{CS}$, is formed by heating ammonium thiocyanate:



This method of preparation is similar to that of urea from ammonium cyanate (151). Thiourea melts at 180° and is soluble in water.

Carbon subsulphide, C_3S_2 , is produced in small quantities when an electric arc is allowed to burn between metal electrodes in carbon disulphide. By distillation in a high vacuum carbon subsulphide is obtained as a bright red, highly refractive liquid (m.p. -0.4°). Carbon subsulphide polymerises very easily to black amorphous products of the composition $(\text{C}_3\text{S}_2)_x$, and in this respect is very similar to carbon suboxide (125).

Carbon oxysulphide, COS , is a colourless, odourless, inflammable gas, which is produced by the interaction of an isocyanate (155) and hydrogen sulphide:



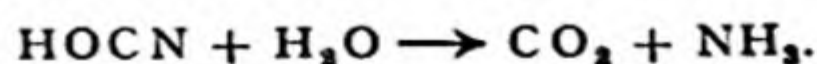
It is also produced by the action of sulphur vapour on carbon monoxide at about 400° . This reaction is reversible.

The formation from isothiocyanates is mentioned in 158. Carbon oxysulphide boils at -50.2° and solidifies at -138.2° . It is very slowly decomposed by water and even by alkalis.

(d) Cyanic acid and its derivatives

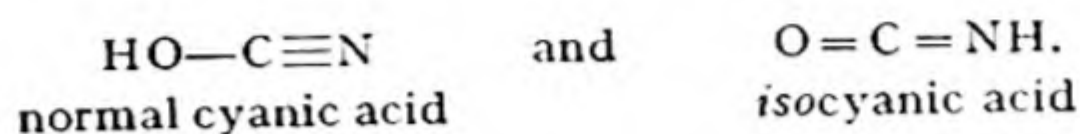
155. *Cyanic acid*, HOCN , may be considered as the simplest hydroxycarbonitrile from which the hypothetical carbonic acid, HOCOOH , should be produced by hydrolysis.

Salts of cyanic acid are produced by oxidation of the corresponding salts of hydrocyanic acid. *Potassium cyanate* is prepared by oxidising potassium cyanide with potassium permanganate. The alkali cyanates are soluble in water. Cyanic acid cannot be prepared by the action of dilute acids on alkali cyanates because cyanic acid is rapidly decomposed by the action of water into carbon dioxide and ammonia:



Anhydrous cyanic acid can be obtained by heating the polymer $(\text{NCOH})_3$, *cyanuric acid*; if the gas produced in this way is rapidly cooled below 0° , a colourless liquid with a penetrating odour is produced, which rapidly polymerises above 0° to another polymer *cyamelide* (156).

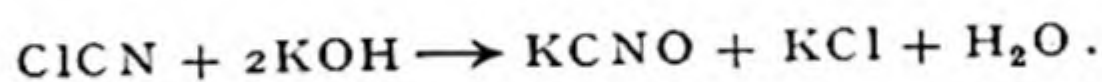
Two possible structures may be postulated for a compound of the composition CHON



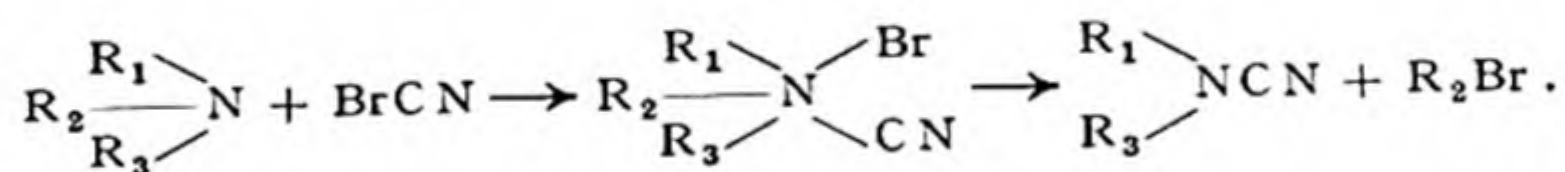
It is not known which of these structures is to be ascribed to free cyanic acid; probably anhydrous cyanic acid consists of a mixture of both tautomeric forms.

Derivatives of both isomers are known.

Cyanogen chloride, CNCl , may be considered as the chloride of normal cyanic acid. It is a liquid of spec. grav. 1.222 at 0° , b.p. 13° , f.p. -1.5° ; it is very poisonous. Cyanogen chloride is prepared by treating hydrocyanic acid or potassium cyanide with chlorine. It readily polymerises to cyanuric chloride, $\text{C}_3\text{N}_3\text{Cl}_3$, especially in the presence of hydrochloric acid. It gives potassium chloride and potassium cyanate with caustic potash:



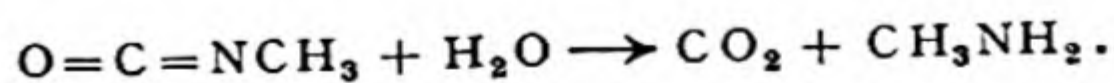
Cyanogen bromide combines with tertiary amines to form addition products, which break down on warming into a dialkylcyanamide and alkyl bromide:



The dialkylcyanamide easily breaks down on hydrolysis into carbon dioxide and a secondary amine. Hence this is a method for converting tertiary amines into secondary amines (VON BRAUN).

Esters of cyanic acid cannot be obtained in a pure state since the polymer, the corresponding *ester of cyanuric acid*, $(\text{NCOC}_2\text{H}_5)_3$, is produced by the action of sodium alcoholate, for example, on cyanogen chloride.

Esters of isocyanic acid, on the other hand, are well known. They are produced by the action of dialkyl sulphates on potassium cyanate. These esters are volatile liquids with an intense, suffocating smell. They polymerise easily to esters of *isocyanuric acid*, e.g. $(\text{OCNC}_2\text{H}_5)_3$. The structure of these compounds follows from their fission by water or dilute alkalis into an amine and carbon dioxide:



WURTZ obtained the first primary amines by means of this reaction in

1848; in this way they are obtained in a pure state uncontaminated with secondary and tertiary amines.

Cyanamide, H_2NCN , is produced, for example, from cyanogen chloride and ammonia; it is a solid, crystalline, hygroscopic material, which polymerises easily. The hydrogen atoms are replaceable by metals, *e.g.* by silver. *Silver cyanamide*, CN_2Ag_2 is yellow and insoluble in dilute ammonia.

Calcium cyanamide is a technically important substance produced by heating calcium carbide in a stream of nitrogen at 1000° . The reaction $\text{CaC}_2 + \text{N}_2 \rightarrow \text{CaCN}_2 + \text{C}$, is exothermic. The crude product, *nitro-lime*, which is dark in colour due to the admixed carbon, is used as an artificial fertiliser, because the combined nitrogen is split off as ammonia in the soil. The nitro-lime can be converted into ammonia also by heating with water under pressure:

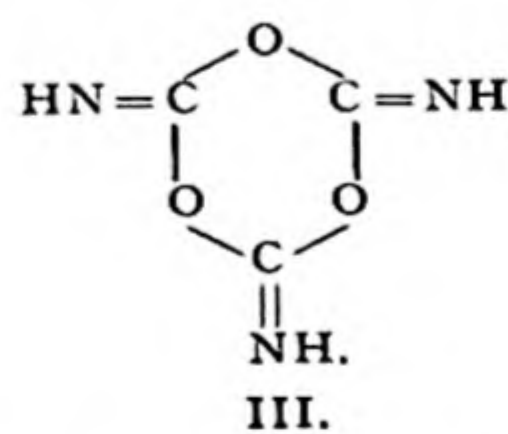
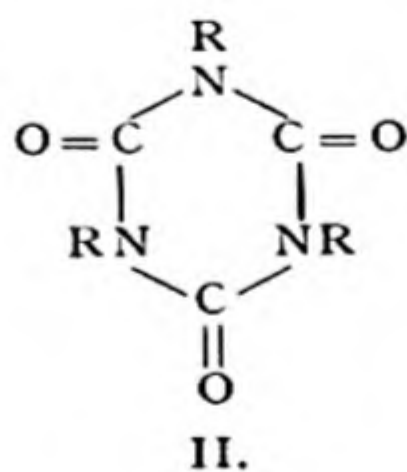
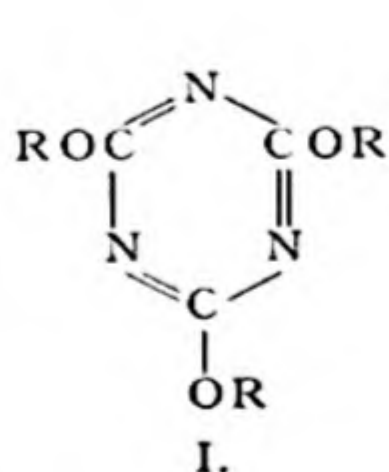


This industry, depending on the fixation of atmospheric nitrogen (FRANK and CARO)' relies on cheap electrical energy on account of the strongly endothermic nature of the formation of calcium carbide (see 91).

When nitro-lime is heated to about 1200° (in presence of sodium chloride as a flux) calcium cyanide is produced; $\text{CaCN}_2 + \text{C} \rightleftharpoons \text{Ca}(\text{CN})_2$. By rapidly cooling the fused mixture (because otherwise the reaction will take the reverse direction) a product with a high calcium cyanide content is obtained, which can be used for the same purposes as an alkali cyanide or worked up into the latter.

156. *Cyanuric acid*, $(\text{NCOH})_3$, is usually prepared by heating urea (151). When potassium ferricyanide is heated with bromine at 220° , the bromide of cyanuric acid is produced and this is converted into cyanuric acid by warming with water.

Two series of esters may be derived from this acid, the *normal* or *O*-esters and the *esters of isocyanuric acid* or *N*-esters. The former are produced from cyanuric bromide (or chloride) and sodium alcoholates. The alkyl groups in these esters are attached to oxygen, because on hydrolysis they give the alcohol and cyanuric acid. Structure I must therefore be ascribed to these esters:



The *isocyanurates* are produced by heating silver cyanurate with alkyl iodides. In these esters the alkyl groups are attached to nitrogen, for on boiling with dilute alkali the substance is split up hydrolytically into a

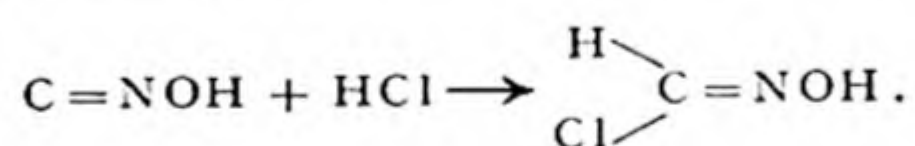
primary amine and carbon dioxide; these esters therefore possess structure II.

When alkyl iodides are allowed to react on the silver salt at ordinary temperatures O-esters are produced; on heating, these pass over into the N-esters. Formula III may represent the structure of cyamelide (155), since this compound is decomposed into carbon dioxide and ammonia by simply boiling with water. A similar ring of oxygen and carbon atoms is to be found in paraldehyde (61).

The relationship between cyanic acid, cyanuric acid and cyamelide is as follows. Cyamelide is the stable modification at ordinary temperatures, but above 150° it passes over into cyanuric acid. Since this transformation takes place very slowly, the position of the transition point cannot be accurately determined. Although cyanuric acid is the metastable modification at ordinary temperatures, it does not change spontaneously into cyamelide, since the velocity of the reaction is too low. When the vapour from cyamelide is rapidly cooled below 0° , the unstable, monomeric form of cyanic acid is produced, which is capable of existence only at low temperatures.

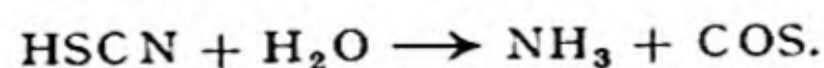
157. *Fulminic acid*, CNOH , is isomeric with cyanic acid. LIEBIG and WÖHLER discovered in 1823, that the compositions of the mercury and silver salts of fulminic acid were the same as those of the corresponding salts of cyanic acid. The fulminates are produced by adding mercury or silver to nitric acid and alcohol in certain proportions (HOWARD). The best known is *mercury fulminate*, $\text{HgC}_2\text{N}_2\text{O}_2$, which explodes when struck. It is used for filling percussion caps or detonators by which gun-cotton and other explosives are made to explode (primer). Since *silver fulminate* is even more explosive than mercury fulminate this is not used in practice.

Fulminic acid is a very unstable, volatile substance with very poisonous properties and an odour similar to that of prussic acid. The structure is probably $\text{C}=\text{NOH}$ (NEF). Hydroxylamine and formic acid are produced by the action of dilute hydrochloric acid. When concentrated hydrochloric acid is allowed to react on fulminic acid with cooling, an addition product is produced according to the equation:



158. *Thiocyanic acid*, HSCN , is very similar in properties to cyanic acid (155) but is more stable towards water. By treating potassium thiocyanate with concentrated sulphuric acid and condensing the vapours produced in a receiver cooled in liquid air, thiocyanic acid is obtained as a colourless solid melting at -110° ; the liquid, however, already changes over into a solid polymer at -90° (BIRCKENBACH).

By warming with dilute sulphuric acid, HSCN takes up a molecule of water and decomposes in a similar way to cyanic acid with the formation of carbon oxysulphide (154):



Potassium thiocyanate, KCNS , is produced by fusing potassium cyanide

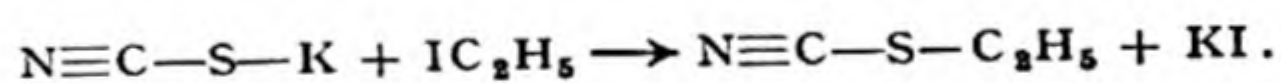
with the calculated quantity of sulphur. It is used for several purposes including the titration of silver by the VOLHARD method.

Silver thiocyanate, AgCNS , is produced by adding silver nitrate solution to a solution of potassium thiocyanate. It is insoluble in dilute mineral acids. *Ferric thiocyanate* is a sensitive test for ferric salts on account of the dark red colour, which is derived from unionised $\text{Fe}(\text{CNS})_3$ molecules, for neither ferric ions nor thiocyanate ions are coloured red in solution. The colour is increased by any treatment which decreases the ionisation, such as by adding more ferric salt or thiocyanate; the red colour is transferred into the organic solvent when the red solution is shaken with ether, which is, of course, incapable of extracting ferric or thiocyanate ions.

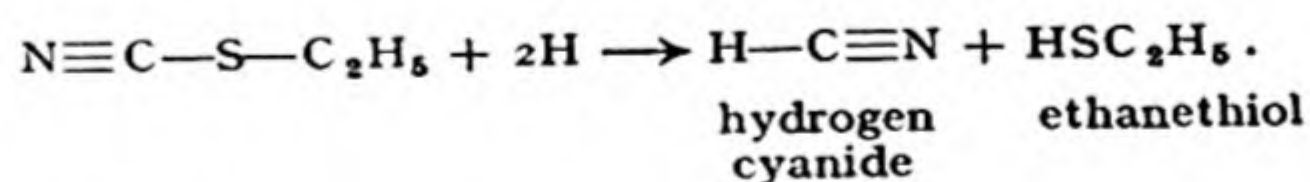
Thiocyanogen, $(\text{CNS})_2$, is formed when silver or lead thiocyanate is treated with a solution of bromine in carbon disulphide; insoluble silver or lead bromide and carbon disulphide containing free thiocyanogen are formed. The latter may be obtained in the form of yellowish white crystals, which melt at -3° . It is unstable at ordinary temperatures and is decomposed by water, but it may be kept in dilute solutions of carbon disulphide, ether or carbon tetrachloride. In these solutions thiocyanogen is similar in behaviour to the halogens; if such a solution is shaken with metals, *e.g.* with zinc or cadmium, the corresponding thiocyanates are formed. Thiocyanogen also adds on easily to substances containing a carbon—carbon double bond.

As with cyanic acid, two series of esters are derived from *thiocyanic acid*, the structure of which is known with no more certainty than that of cyanic acid *viz.*, the *thiocyanates* $\text{N}\equiv\text{C}-\text{S}-\text{R}$ and the *isothiocyanates* $\text{S}=\text{C}=\text{N}-\text{R}$.

The thiocyanate esters are produced from metal thiocyanates and alkyl iodides:



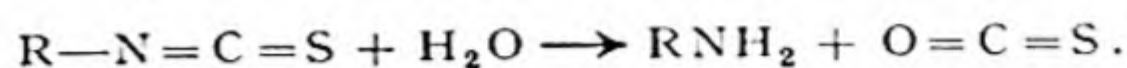
They are liquids with a garlic-like smell, which are insoluble in water. It may be shown both by reduction and by oxidation that in these compounds the alkyl group is attached to sulphur. On reduction, a thiol (43) is produced along with hydrocyanic acid, which gives methylamine on further reduction:



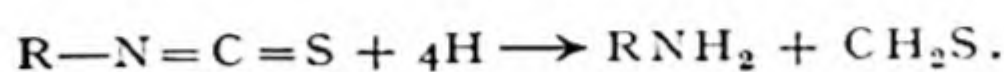
Alkane sulphonic acids, *e.g.* $\text{C}_2\text{H}_5\text{SO}_3\text{H}$ (45), are produced by oxidation. On heating, thiocyanates are converted into isothiocyanates. *Allyl thiocyanate*, NCSC_2H_5 , already does so on distillation.

The *isothiocyanates* are also called *mustard oils*. In these compounds the alkyl group is attached to nitrogen. They possess the structure $\text{S}=\text{C}=\text{N}-\text{R}$,

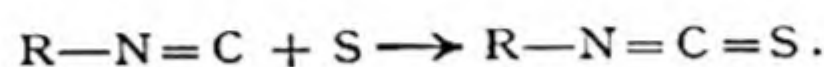
as appears from the following reactions. Under the influence of concentrated sulphuric acid they take up water and give primary amines and carbon oxysulphide:



Primary amines are also produced on reduction along with *trithiomethene*, $(\text{CH}_2\text{S})_3$, which is very probably produced from thiomethene CH_2S (unknown in the free state) formed initially, by polymerisation:



Isothiocyanates are also produced by the action of sulphur on carbylamines (56):



They occur in the free state or combined as glucosides (179) in plants. Mustard seed (*Cinapis nigra* L.) contains a glucoside of complicated composition, the potassium salt of *myronic acid*; this is split up by acids or by an enzyme occurring in the seed, into glucose, potassium bisulphate and *allyl iso-thiocyanate*.

(xi) SUGARS; CARBOHYDRATES OR SACCHARIDES

159. Besides sugars like glucose, fructose, cane-sugar, milk-sugar, etc., substances such as starch and cellulose, which possess properties quite different from those of the sugars, also belong to this group of compounds. The name *carbohydrates* is taken from the elementary composition of most of these compounds, which can be expressed by the general formula $\text{C}_m(\text{H}_2\text{O})_n$.

Apart from the fact that in more recent times sugars have been discovered with compositions which no longer agree with this formula, *e.g.* the methylpentoses, the name carbohydrate is likely to give the totally wrong impression that these substances are to be regarded as hydrates of carbon, in much the same way, for example, as one thinks of the known hydrate of chlorine. The name carbohydrate has persisted mainly in physiological literature; these compounds are better designated by the name of *saccharides*.

This class of compounds is divided into two main groups. The first comprises substances, which cannot be split up into simpler compounds still possessing all the characteristics of the group; these compounds are called *monosaccharides*. The second main group comprises substances, which can be split up into monosaccharides by hydrolysis; the compounds in this group are called *polysaccharides*. The main group of polysaccharides can again be divided into two sub-groups:

1. Compounds, in which the molecule is built up of a small number of

monosaccharides. If this number is two, the substance is called a *disaccharide*, (172) of which cane-sugar, malt-sugar and milk-sugar are examples. The disaccharides, like the much less well known tri- and tetra-saccharides, (178) show a great similarity to the simple sugars, *e.g.* as regards taste, solubility in water and chemical behaviour.

2. Compounds in which the molecule is built up of a large number of monosaccharide residues. In their physical properties these substances show no resemblance to the sugars. They are either insoluble in water like cellulose, (186), or they give colloidal solutions with water like starch (181) and related substances.

(a) *Monosaccharides*

The monosaccharides are denoted by the ending "ose" attached to the greek or latin root giving the number of oxygen atoms, *e.g.* tetrose, pentose, hexose, heptose, nonose, etc. These compounds are differentiated further into two groups the *aldoses* and the *ketoses* according to whether they are similar in structure to aldehydes or ketones. The individual members are spoken of, for example, as aldohexose, ketohexose, etc. By gentle oxidation, *e.g.* with bromine water, monobasic acids are produced from aldoses with the same number of carbon atoms. In this way *pentonic acids* ($C_5H_{10}O_6$) are produced from pentoses ($C_5H_{10}O_5$), *hexonic acids* ($C_6H_{12}O_7$) from hexoses ($C_6H_{12}O_6$), etc. Dibasic acids with the same number of carbon atoms are produced from aldoses by oxidation with concentrated nitric acid. In such cases the molecule is oxidised at both ends. Ketoses give acids with a smaller number of carbon atoms on oxidation.

Both aldoses and ketoses are converted into the corresponding alcohols by reduction (two hydrogen atoms taken up), pentitols $C_5H_{12}O_5$, are produced from pentoses and hexitols, $C_6H_{14}O_6$, from hexoses, etc.

Four reactions are known, which are shown by all monosaccharides.

1. When an aqueous solution of a monosaccharide is warmed with an ammoniacal silver solution, a silver mirror is deposited on the walls of the reaction vessel.

2. An aqueous solution of a monosaccharide is coloured first of all yellow and then brown when warmed with alkali. In this test the sugar is converted into resinous products.

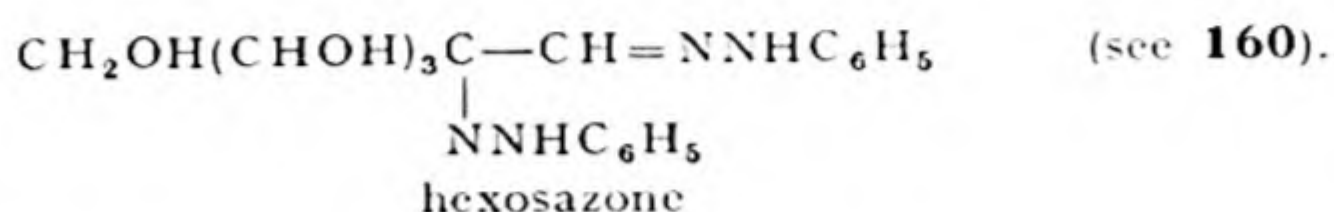
3. An alkaline copper solution, such as FEHLING'S or OST'S solution, is reduced by warming with a solution of a monosaccharide and yellowish red cuprous oxide separates.

In TROMMER'S test a monosaccharide is dissolved in dilute caustic soda, a few

drops of copper sulphate solution are added and a blue colour is produced. On warming cuprous oxide is precipitated.

In these reactions monosaccharides show a great similarity to aldehydes. Thus all monosaccharides have a *reducing group* in the molecule.

4. On warming with phenylhydrazine, $C_6H_5NHNH_2$, monosaccharides form beautifully crystalline, yellow compounds, called *osazones* which are insoluble in water:



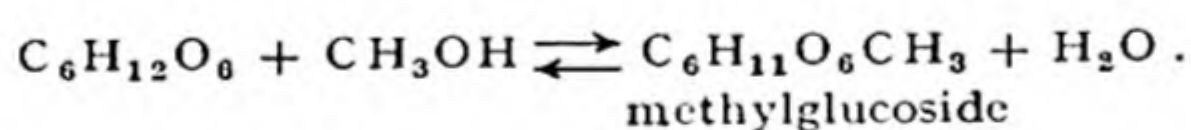
Structure of the monosaccharides

160. Aldoses. The structure of the aldohexoses of the molecular formula $C_6H_{12}O_6$ is derived from the following data:

1. Nearly all hexoses contain a normal carbon chain; thus a hexitol, sorbitol, is produced from glucose, for example, by reduction with sodium amalgam and this is converted into 3-iodohexane, $CH_3CH_2CHICH_2CH_2CH_3$, on more vigorous reduction (with hydriodic acid). The iodo-compound can be converted into an alcohol from which *hexan-3-one* is produced by oxidation, while further oxidation produces *n*-butyric acid and acetic acid. This proves the presence of a normal carbon chain in the 3-iodohexane and therefore in the hexose also.

2. In a hexose, five of the oxygen atoms are present in the form of hydroxyl groups because a penta-acetate is formed by warming with acetic anhydride (and a little zinc chloride or sodium acetate).

3. When a hexose is boiled with methanol, in which a little hydrogen chloride is dissolved, the following reaction occurs:

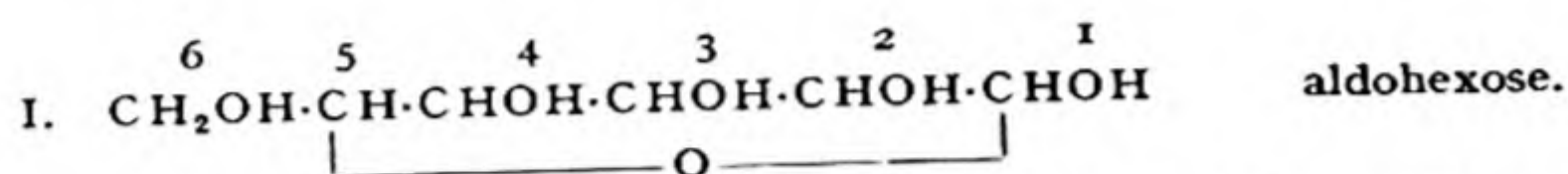


Hence a hydrogen atom in the glucose molecule, for example, is replaced by $-CH_3$. A similar reaction takes place with other alcohols. This reaction is similar to the formation of acetals from aldehydes (see 60). The compounds formed are called *glucosides* (179) and are easily split up into hexose and alcohol again by hydrolysis. The aldehydic properties of the hexoses are no longer present in the glucosides; they have no reducing properties and they do not react with phenylhydrazine.

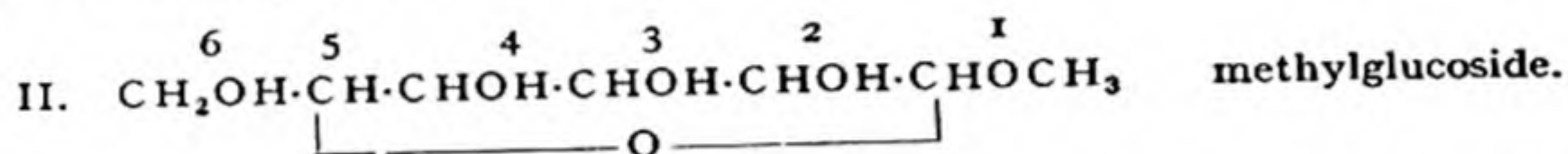
By the action of dimethyl sulphate and caustic soda, followed by treatment with methyl iodide and silver oxide, methylglucoside can be methylated further, four more hydrogen atoms being replaced by methyl groups with the production of a tetramethylmethylglucoside $C_6H_7O(OCH_3)_5$. When

this substance is warmed with dilute sulphuric acid, only one methyl group is split off hydrolytically; methanol is produced and a tetramethylglucose possessing reducing properties like glucose itself (PURDIE, IRVINE, HAWORTH, 1920—1930). This methyl group is apparently the same as that which can be easily introduced into glucose with the elimination of water by the action of methanol.

From the foregoing it appears, that four of the five hydroxyl groups in the hexoses have the same properties. The different properties of one hydroxyl group must be connected with a particular method of combination for this hydroxyl group and is expressed by the following structural formula (HAWORTH):

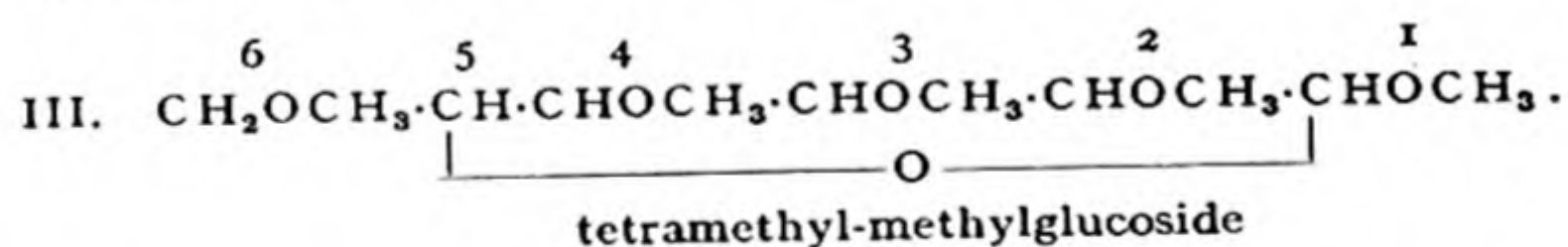


The hydroxyl group on carbon atom 1 reacts with methanol with the formation of a *methylglucoside*:



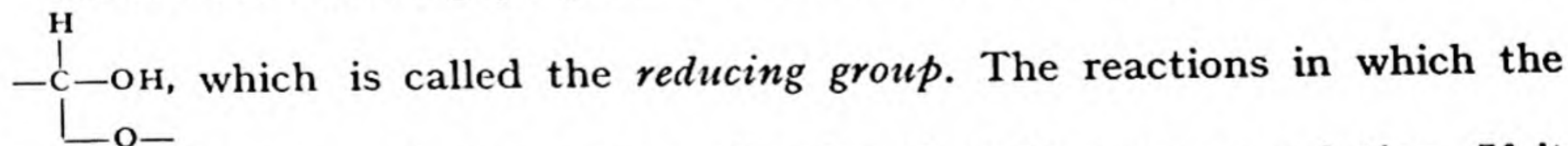
It is understandable why the methyl group in the methylglucoside can be split off by hydrolysis, since the carbon atom 1 is combined to a second oxygen atom (compare esters, 77 and acetals 60).

The methyl groups in tetramethylmethylglucoside, which are attached through oxygen atoms, to carbon atoms 2, 3, 4 and 6, are not split off by hydrolysis, since each of these carbon atoms is attached to one oxygen atom only. Hence the mode of combination of these methyl groups to the respective carbon atoms is similar to the mode of attachment in an ether ROCH_3 .

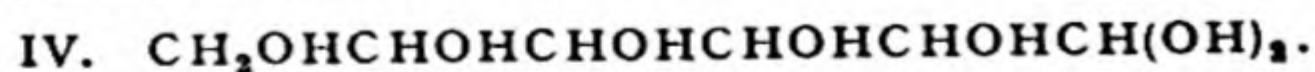


The oxygen atom attached to carbon atoms 1 and 5 is called the *epoxy-oxygen* atom.

Hence the reducing properties of an aldohexose depend on the group

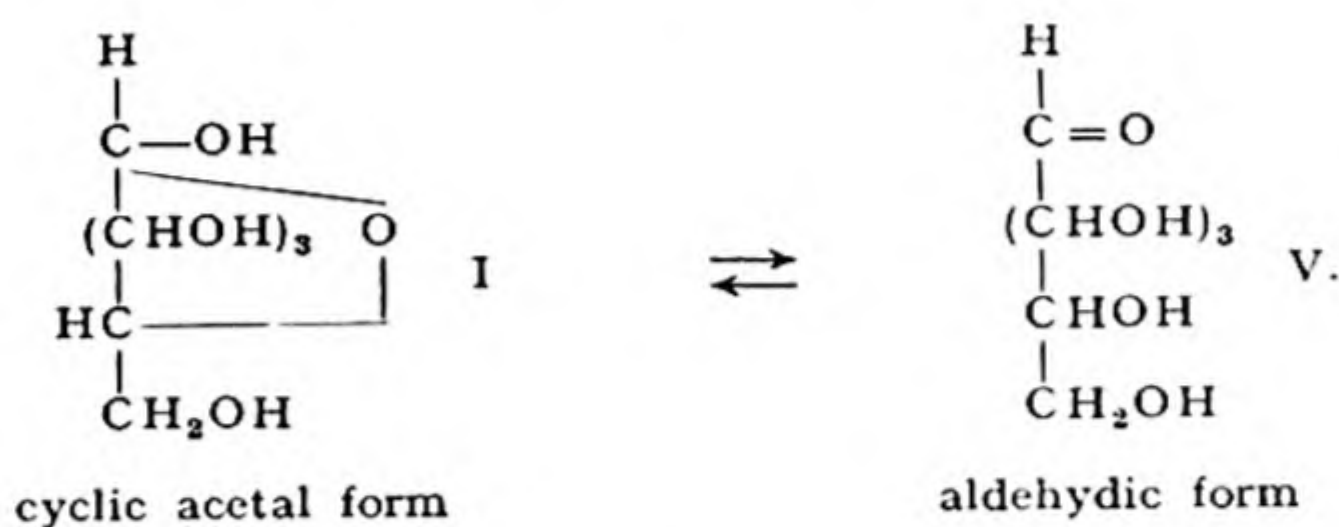


hexoses have a reducing action all take place in aqueous solution. If it is assumed that the hexoses can add on a molecule of water, a compound is formed with the formula:



Compounds containing the $-\text{CH}(\text{OH})_2$ group show only some of the reactions of aldehydes, including reducing power (see 128). Likewise, the monosaccharides fail to give all the reactions of aldehydes. They give no colour with SCHIFF's reagent, fuchsin—sulphurous acid, they do not combine with sodium bisulphite, nor do they polymerise. This is in agreement with the above formulation.

It may also be assumed that in an aqueous solution of an aldohexose, an equilibrium between two forms is present:

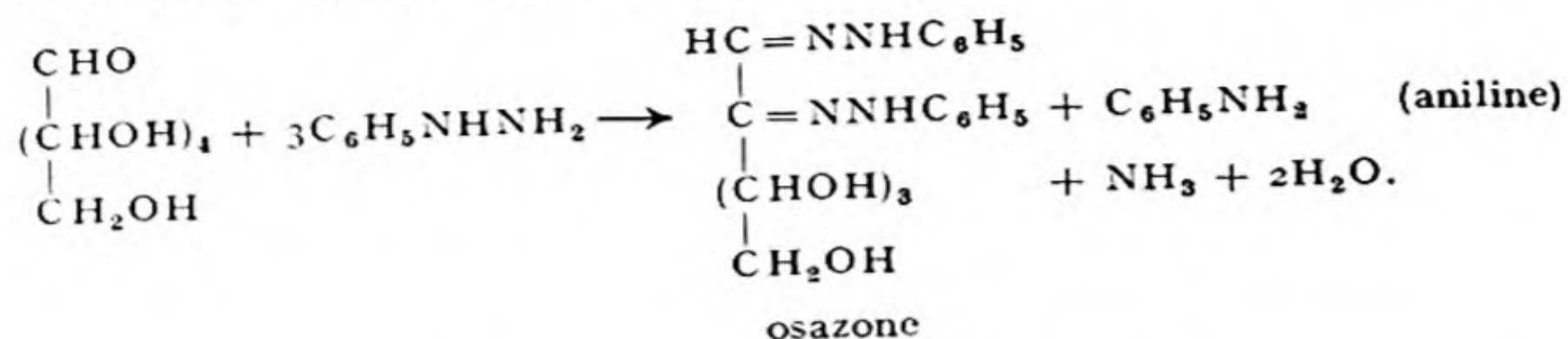


Isomeric penta-acetates of glucose are known, one of which is derived from the cyclic acetal form (I) and the other from the aldehydic form (V). Acetates of the aldehydic forms are known also in the cases of galactose, arabinose and xylose.

The ultra-violet absorption spectrum of an aqueous solution of glucose, galactose or arabinose, does not show the band characteristic for the aldehyde group (59, 62). From this it may be concluded that the aldehydic form of the monosaccharides is present in these solutions only in very low concentrations. This is confirmed by the similarity of the absorption spectrum of methylglucoside.

It should be mentioned that a cyclic acetal formula had already been suggested for the aldoses in 1883 by TOLLENS on the basis of the observation that these compounds did not show all the reactions of the aldehydes.

The formation of osazones occurs as follows. By the action of phenylhydrazine, $\text{C}_6\text{H}_5\text{NHNH}_2$, a hydrazone, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{H}=\text{NNHC}_6\text{H}_5$, is first of all produced. Thus the hexose reacts according to formula V. In most cases the hydrazones of the hexoses are readily soluble and they are not therefore precipitated. By the action of an excess of phenylhydrazine, the HCOH group situated next to the terminal carbon atom is converted into a $-\text{CO}-$ group, a molecule of phenylhydrazine being reduced to ammonia and aniline, $\text{C}_6\text{H}_5\text{NH}_2$. The newly produced $-\text{CO}-$ group then reacts with a third molecule of phenylhydrazine and the sparingly soluble osazone separates:

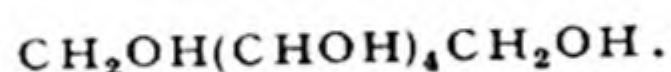


The proof that the phenylhydrazine residues in the osazones are attached to carbon atoms 1 and 2 is given in 165.

It has already been mentioned that a monobasic acid with six carbon atoms is produced on careful oxidation of an aldohexose; actually it is not the acid itself but the corresponding lactone, which $\text{CH}_2\text{OHCH}(\text{CHOH})_3\text{C}=\text{O}$, [O] is formed, in agreement with the annexed formula.

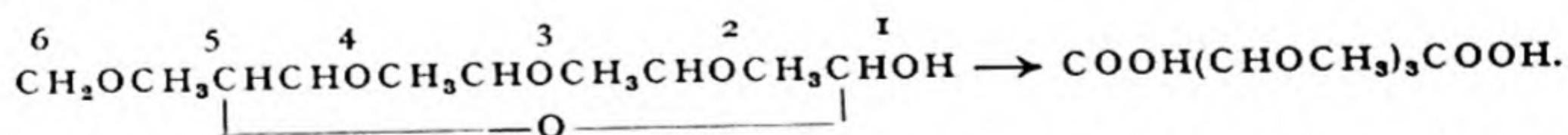
On reduction of a hexose to a hexitol, an atom of hydrogen is taken up on carbon atom 1, by which the bond between this atom and the epoxy-oxygen atom is broken, while the latter also takes up an atom of hydrogen, so that a hydroxyl group is produced on carbon atom 5.

In the hexitols, only one hydroxyl group is attached to each of the carbon atoms, for, if one carbon atom were to carry two hydroxyl groups, the hexitol would have the properties of an aldehyde or a ketone, since compounds containing the grouping $-\text{C}(\text{OH})_2-$, easily split off water. The hexitols possess exclusively alcoholic properties, so that the formula of the hexitols is



From this it follows, that in the hexoses also, no two hydroxyl groups can be attached to one carbon atom, as is assumed in formulae I and V.

It is assumed further in formula I, that the epoxy-oxygen atom is attached to carbon atoms 1 and 5. This has been proved in the case of glucose as follows. Trimethoxypropane 1,3-dicarboxylic acid (trimethoxyglutaric acid) is produced on oxidising tetramethylglucose with nitric acid. Since it may be assumed that the carbon chain is broken at the carbon atom carrying the epoxy-oxygen atom and the oxidation product contains a chain of five carbon atoms, the epoxy-oxygen atom must be attached to carbon atoms 1 and 5:

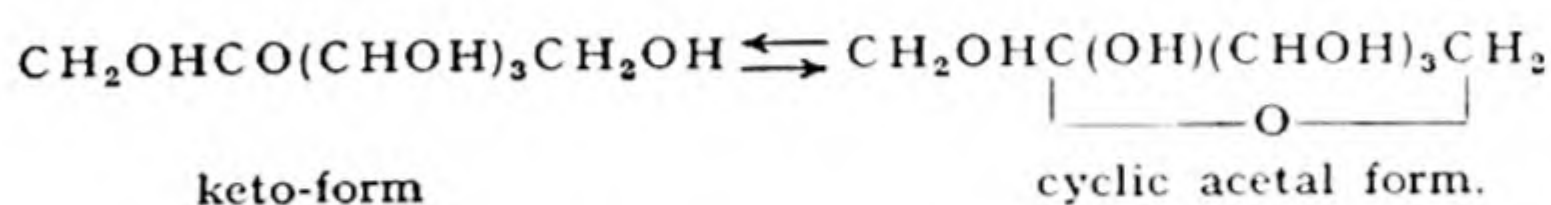


This oxidation is carried out on tetramethylglucose rather than on glucose itself, because the methoxyl groups are more stable than hydroxyl groups, so that any alteration in the mode of combination of the epoxy-oxygen atom during the oxidation of the methyl derivative, can be excluded. It may now be assumed that the epoxy-oxygen atom in glucose is also combined

with carbon atoms 1 and 5. This mode of combination occurs also in a number of other monosaccharides, as is proved in a similar way, by methylation and subsequent oxidation. The molecules of these sugars therefore contain a ring of five carbon atoms and one oxygen atom, *i.e.* a *pyran ring*. Sugars with this structure are therefore called *pyranoid* sugars or *pyranoses* (HAWORTH).

Some sugars are known in which the epoxy-oxygen atom is attached to carbon atoms 1 and 4. Thus these contain a ring of four carbon atoms and one oxygen atom, a *furan ring*, and are therefore called *furanoid* sugars or *furanoses*.

161. Ketoses. The most important ketohexose is *fructose*:



When fructose is oxidised with mercuric oxide in presence of barium hydroxide, glycollic acid, CH_2OHCOOH , and trihydroxybutyric acid, $\text{CH}_2\text{OH}(\text{CHOH})_3\text{COOH}$, are produced. Thus in this oxidation the carbon chain is broken in agreement with the above ketonic formula. On the same reasoning as given for the aldohexoses, it is assumed that fructose can occur in an isomeric form having a cyclic structure and that both forms are present in equilibrium in solution.

The structure of fructose may also be proved as follows. By the addition of hydrogen cyanide followed by hydrolysis, a heptonic acid is produced,

which must have the structure: $\overset{1}{\text{CH}_2\text{OH}}\overset{2}{\underset{\text{COOH}}{\text{C}}}(\text{OH})(\text{CHOH})_3\text{CH}_2\text{OH}$, if the doubly

bound oxygen atom occurs on carbon atom 2 in fructose. The structure of this heptonic acid is proved as follows. It is reduced by hydriodic acid to hexane 2-carboxylic acid, $\text{CH}_3\text{CH}(\text{CH}_2)_3\text{CH}_3$, the structure of which has been proved by synthesis.

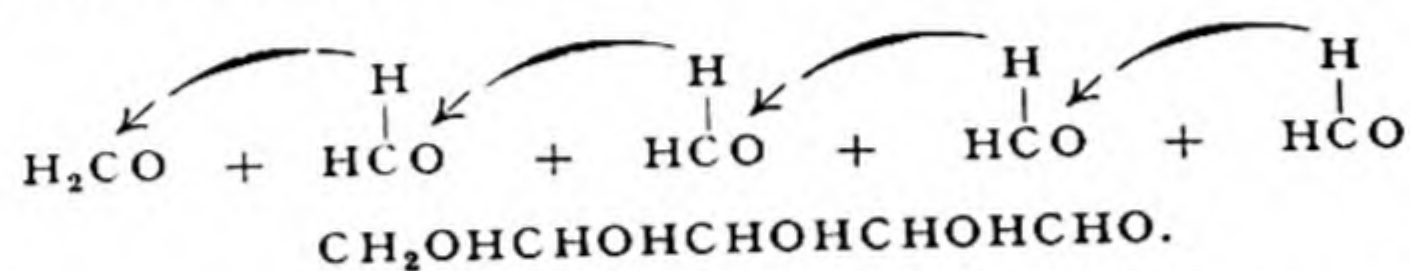
Like the aldoses, ketoses also reduce ammoniacal silver solutions and alkaline copper solutions.

Methods of formation of the monosaccharides

162. Monosaccharides can be obtained 1. by the hydrolysis of polysaccharides (180) or glucosides (see 179) by the action of dilute acids or enzymes (207). Polysaccharides containing both hexoses and pentoses (*pentosans*) are very widely distributed throughout the vegetable kingdom. 2. By oxidising the corresponding alcohols, for example with nitric acid. Thus *mannose* ($\text{C}_6\text{H}_{12}\text{O}_6$) is obtained in this way from mannitol ($\text{C}_6\text{H}_{14}\text{O}_6$) (113). 3. From

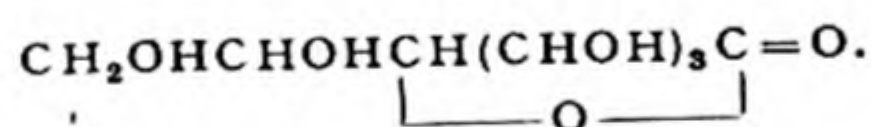
brominated aldehydes by replacing the bromine atom by hydroxyl by means of baryta water. In this way, from bromoethanal, CH_2BrCHO , the simplest possible sugar, glycolaldehyde, CH_2OHCHO , (m.p. 97° with decomposition), is produced. This shows all the reactions of a monosaccharide and in addition easily forms a polymeride and is volatile with steam. 4. By the action of lime-water on a solution of formaldehyde, a sweet, syrupy liquid is produced, which contains hexoses amongst other things (BUTLEROW, LOEW). The reaction takes place much more rapidly when a strong solution of formaldehyde is warmed with methanol and calcium hydroxide. Besides hexoses, the reaction product also contains pentoses and tetroses, which can be isolated as the osazones. The osazone of *dl*-glucose is obtained as the main product.

In this case the methanal undergoes an aldol condensation (61):



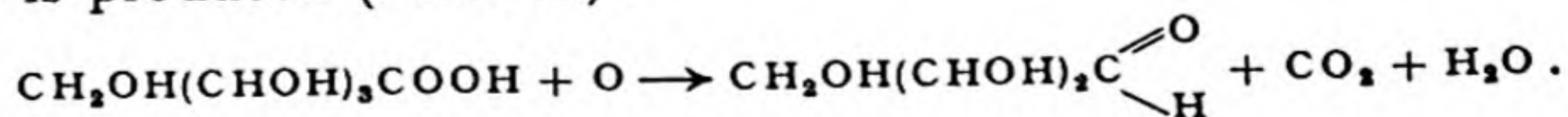
By the addition of bromine to propenal (acrolein, 97), $\text{CH}_2\text{BrCHBrCHO}$ is obtained, which is converted by cold baryta-water into 1,2-dihydroxypropanal or glyceraldehyde, $\text{CH}_2\text{OHCHOHCHO}$, from which hexoses are produced by the continued action of baryta-water (aldol condensation): the osazone of *dl*-glucose can be isolated from the reaction product.

5. Methods are also known for converting sugars into monosaccharides containing one more carbon atom (KILIANI, E. FISCHER). An aldohexose can add on hydrogen cyanide. The addition product, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{CHOHCN}$, on hydrolysis gives a monobasic polyhydroxy-acid with seven carbon atoms, which is readily converted into a lactone:

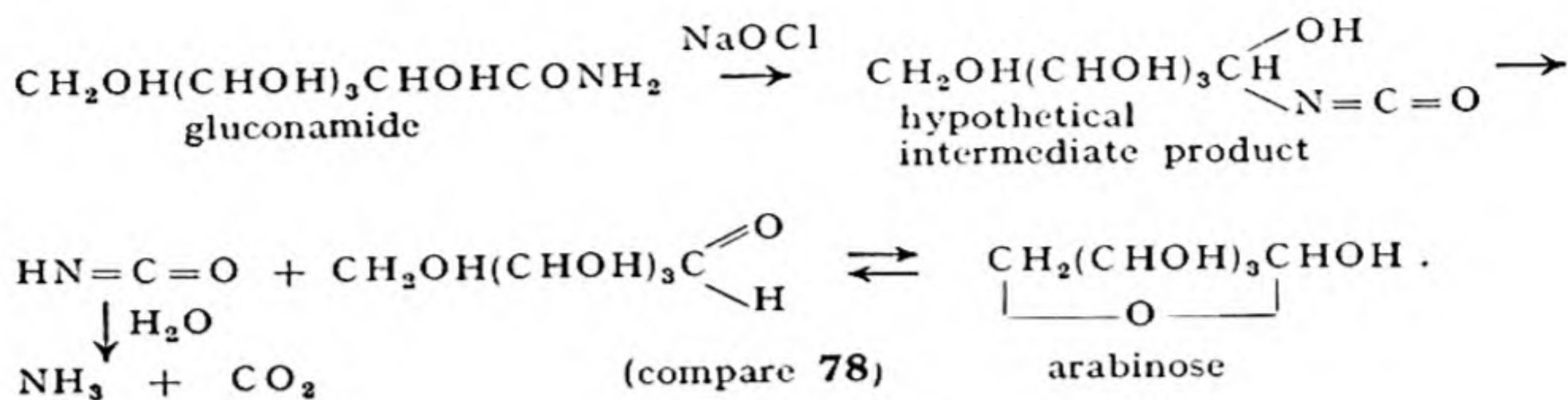


This lactone can be reduced to the corresponding heptose by means of sodium amalgam in aqueous solution. In this way, aldoses with up to ten carbon atoms (and therefore with ten oxygen atoms also), *i.e.* decoses, have been made.

6. Besides the methods of synthesising monosaccharides, methods are also known by which lower monosaccharides are obtained by the degradation of higher members. When the calcium salts of hexonic or pentonic acids are treated with hydrogen peroxide in the presence of ferric salts, a pentose or a tetrose is produced (FENTON):



In the method described by WEERMAN, the amide of a hexonic or a pentonic acid is treated with sodium hypochlorite when the following reactions take place:



Tetroses, pentoses, hexoses and heptoses

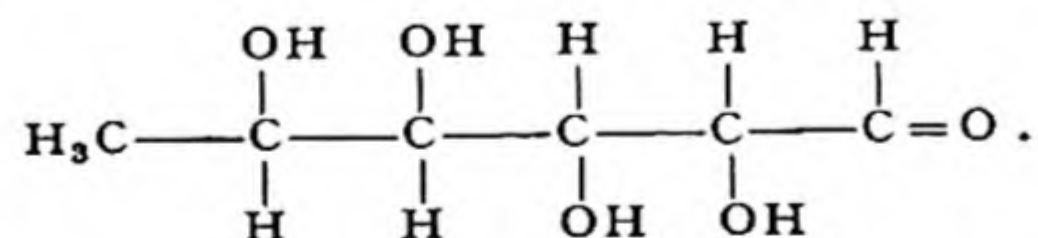
163. *Tetroses* are not found in the vegetable kingdom; *d*- and *l*-erythrose are obtained by the degradation of *d*- and *l*-arabonic acid and *d*-threose by the degradation of *d*-xylonic acid.

Pentoses are produced by the hydrolysis of pentosans (162). Thus *xylan*, occurring in straw and wood, produces by hydrolysis with dilute acids *d*-xylose, which melts at 154°, tastes sweet and shows a decreasing mutarotation. The final value is $[\alpha]_D = +19^\circ$. This sugar can be prepared from wheat straw by treatment with hydrochloric acid.

l-Arabinose can be prepared from cherry-gum, gum arabic or from cotton seed hulls, by boiling these substances with dilute acids by which the polysaccharide *araban* is hydrolysed. *l*-Arabinose melts at 160° and shows a decreasing mutarotation, final value $[\alpha]_D = +105^\circ$. *dl*-Arabinose occurs in the urine of sufferers from pentosuria. *d*-Arabinose, which is laevo-rotatory, has been observed as a fission product of a glucoside (179) in certain species of aloe.

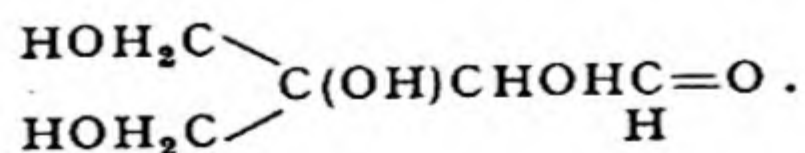
d-Ribose, m.p. 95°, is a laevo-rotatory pentose, which is obtained as a fission product of nucleic acids (394).

l-Rhamnose is an example of a methylpentose. This sugar, which is found as a fission product of various glucosides occurring in the vegetable kingdom, has the formula (aldehydic form):



l-Rhamnose melts at 122–124°; $[\alpha]_D = +8.4^\circ$ (final value).

Apiose is an example of a sugar with a branched chain:



This structure is derived as follows; the monobasic acid, apionic acid, obtained by the careful oxidation of apiose, can be converted into isovaleric acid (72) by reduction with hydriodic acid.

Apiose is produced along with *d*-glucose, by the hydrolysis of apiin, a glucoside occurring in parsley.

On warming with dilute sulphuric acid or hydrochloric acid pentoses give a volatile compound, $C_5H_4O_2$, *furfuraldehyde* (see 312), which gives a red colouring matter with aniline and hydrochloric acid. This is a characteristic reaction for pentoses and pentosans. The pentoses cannot be fermented.

Hexoses are colourless, sweet-tasting substances, which are very soluble in water, sparingly soluble in ethanol and insoluble in ether. They cannot be distilled, since they decompose on heating.

d-Glucose or *grape sugar*, also called *dextrose*, occurs in very many plants, particularly in the juices of sweet fruits, *e.g.* in grapes, apples and pears, and also in seeds and roots. Blood and also urine contain very small quantities of glucose; the urine of sufferers from diabetes mellitus contains considerable quantities of *d*-glucose. Starch (181), glycogen (184) and cellulose (186) give *d*-glucose exclusively on hydrolysis. *d*-Glucose is produced by splitting a number of disaccharides and many glucosides (see 179) and is prepared on a commercial scale by boiling starch with dilute acids (for α - and β -forms of glucose see 168). *d*-Glucose is broken down into ethyl alcohol and carbon dioxide by yeast (see 31). *l*-Glucose is not met with in nature.

d-Mannose occurs in the free state in some plants; the *mannans* are very widely distributed throughout the vegetable kingdom. They are polysaccharides (180) from which *d*-mannose is produced by hydrolysis; thus *d*-mannose can be prepared from the shells of the ivory-nut. Mannose gives a phenylhydrazone, which is very sparingly soluble in water, by which it can be recognised, since the phenylhydrazones of the other monosaccharides are very soluble in water. α - ($[\alpha]_D = +30^\circ$) and β - forms ($[\alpha]_D = -17^\circ$) of *d*-mannose are known (see 168). *d*-Mannose is fermented to alcohol and carbon dioxide by yeast (see 31).

d-Galactose is produced by the hydrolysis of milk-sugar and raffinose. Polysaccharides, the so called *galactans*, occur in the vegetable kingdom, from which galactose is produced on hydrolysis. Anhydrous *d*-galactose melts at 164° and shows mutarotation (see 168), the final value being $[\alpha]_D = +81^\circ$. *d*-Galactose can be fermented.

d-Fructose, also called *laevulose*, occurs in the free state in sweet fruits. Inulin (185) gives only *d*-fructose on hydrolysis. *d*-Fructose is produced along with *d*-glucose by the hydrolysis of sucrose. Aqueous solutions of *d*-fructose are laevorotatory $[\alpha]_D = -93^\circ$; *d*-fructose can be fermented. The rotation decreases considerably with rise in the temperature.

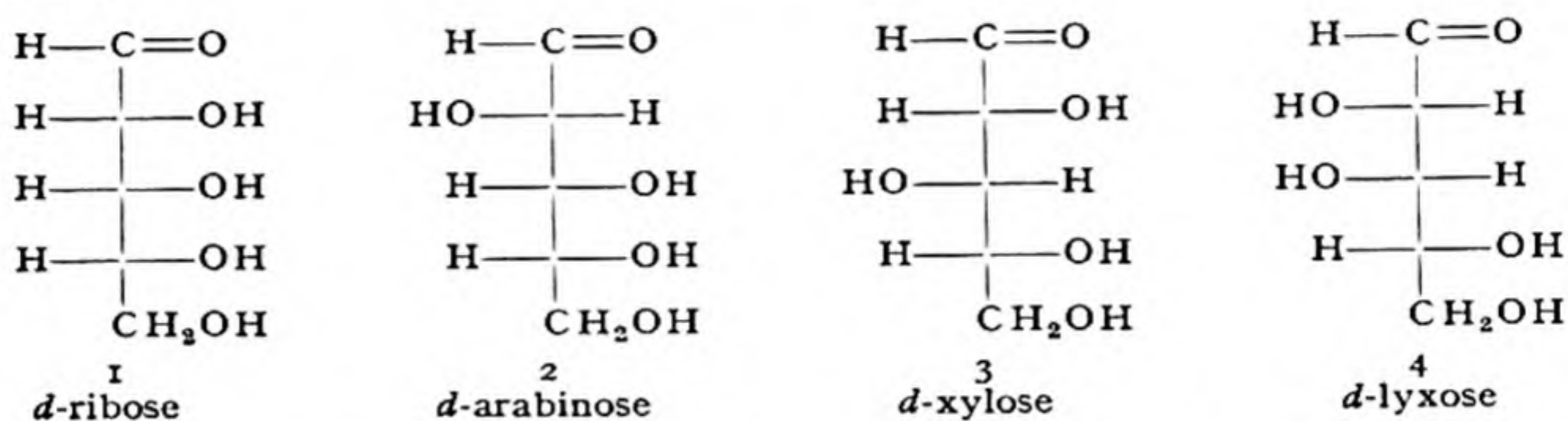
l-Sorbitose can be obtained by the action of sorbose-bacteria on the juice of rowan berries, by which the *d*-sorbitol present in this juice is oxidised to *l*-sorbitose. Sorbitose melts at 165° , has $[\alpha]_D = -42.9^{\circ}$ and is not decomposed by yeast.

Heptoses are prepared synthetically from hexoses. Some are also found in the vegetable kingdom.

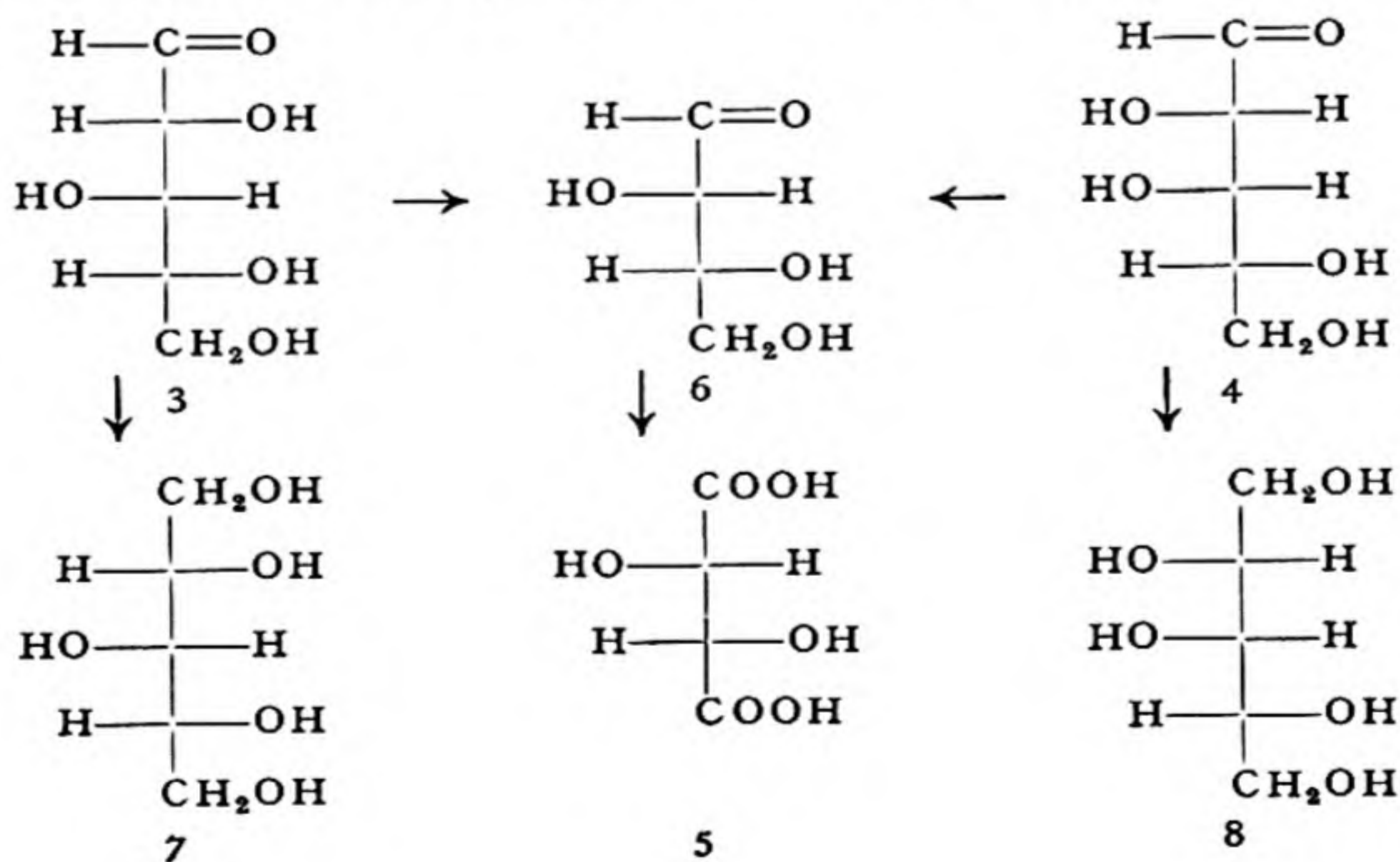
Determination of the stereochemical configuration of the monosaccharides

164. The principles on which the stereochemical configuration depends are discussed in (142).

For determining the stereochemical configuration of the *aldopentoses*, for the present, the occurrence of α - and β -forms for each monosaccharide will be ignored and a start is made with the aldehydic formula as the basis. In this formula three asymmetric carbon atoms are present, which corresponds with eight stereochemical configurations. Hence all the possible forms are known, viz. the dextro- and laevo-rotatory forms of *ribose*, *arabinose*, *xylose* and *lyxose*:



From dextro-rotatory xylose, which is prepared by the hydrolysis of xylan (162), a tetrose (one of the two threoses) can be obtained by degradation, which can be converted into *l*(—)-tartaric acid by oxidation. Since *l*(—)-tartaric acid has configuration 5, it follows that this threose has configuration 6 and dextro-rotatory xylose either 3 or 4:

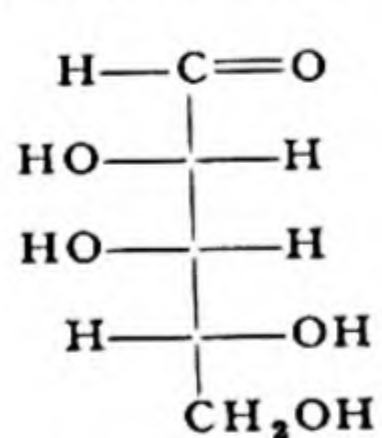
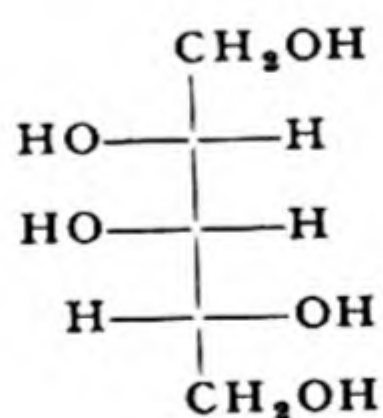
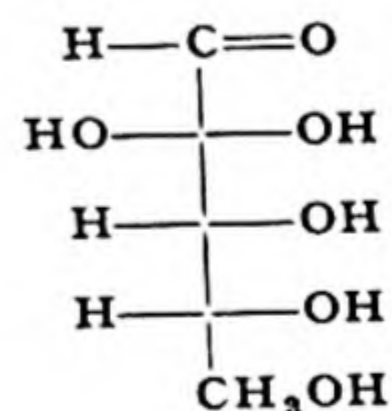
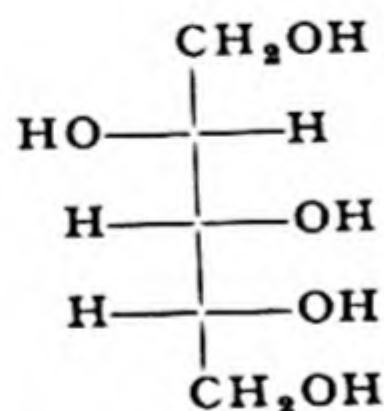


Dextro-rotatory xylose is converted by reduction into an optically inactive pentitol. Configuration 7 must be assigned to this pentitol, since this formula is identical with its mirror image (7 can be made to coincide with its mirror image by rotation in the plane of the paper); the space model of 7 has a plane of symmetry. Hence configuration 3 must be assigned to dextro-rotatory xylose; the pentose 4 should give an optically active pentitol 8 on reduction.

The prefix *d* is now chosen arbitrarily for dextro-rotatory xylose 3 and this sugar is designated *d*(+)-xylose; the antipode of this sugar, which does not occur in nature, is *l*(-)-xylose. The prefix *d* is assigned on the basis of the position of the OH-group attached to the carbon atom carrying the CH₂OH-group; if this OH-group lies to the right in the projection formula, then the sugar is referred to as a *d*-sugar. This classification proposed by ROSANOFF and also by WOHL and FREUDENBERG in most cases agrees with the earlier classification of E. FISCHER, in which those sugars were designated as *d*-sugars which were related either by synthesis or by degradation to *d*-glucose occurring in nature.

The osazone of *d*(+)-xylose is identical with the osazone of laevo-rotatory lyxose, a sugar which is obtained by the degradation of dextro-rotatory galactose. In the formation of osazones, phenylhydrazine residues become attached to carbon atoms 1 and 2, while the remainder of the molecule remains unchanged, which follows for example, from the identity of the osazones from *d*(+)-glucose and *d*(+)-mannose (see page 265). From this it follows that configuration 4 must be assigned to lyxose. This sugar is therefore *d*(-)-lyxose.

By reducing this sugar, a pentitol is produced, which is also obtained from a laevo-rotatory arabinose (163); from this it follows that this arabinose belongs to the *d*-series and must be designated *d*(-)-arabinose (configuration 3).

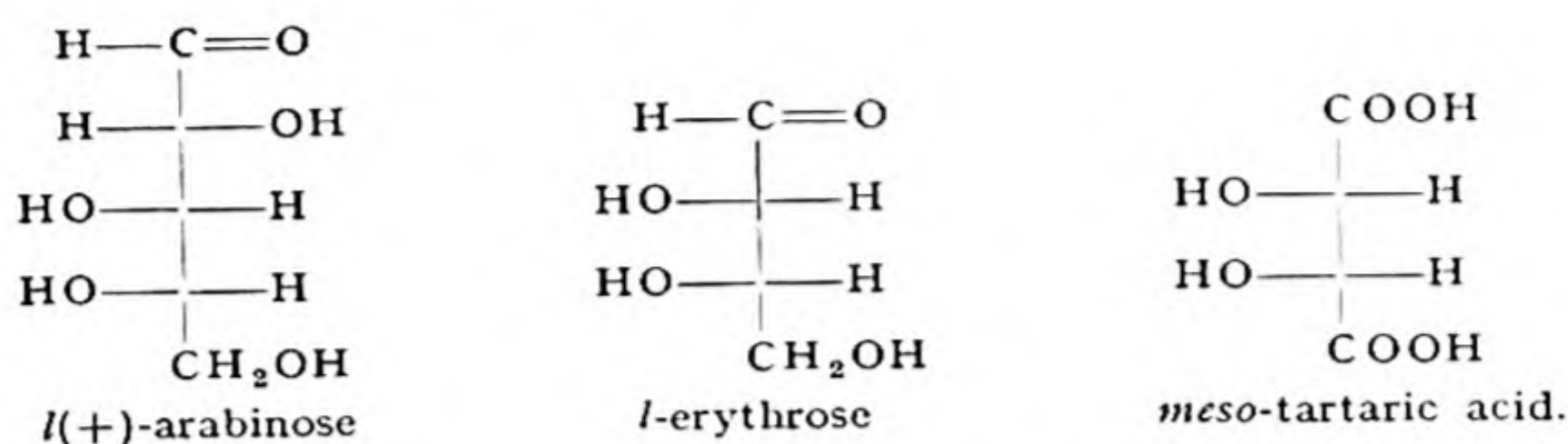
4 *d*(-)-lyxose*d*-arabitol or *d*-lyxitol3 *d*(-)-arabinose.

The dextro-rotatory antipode of *d*(-)-arabinose therefore belongs to the *l*-series and is *l*(+)-arabinose (see 163).

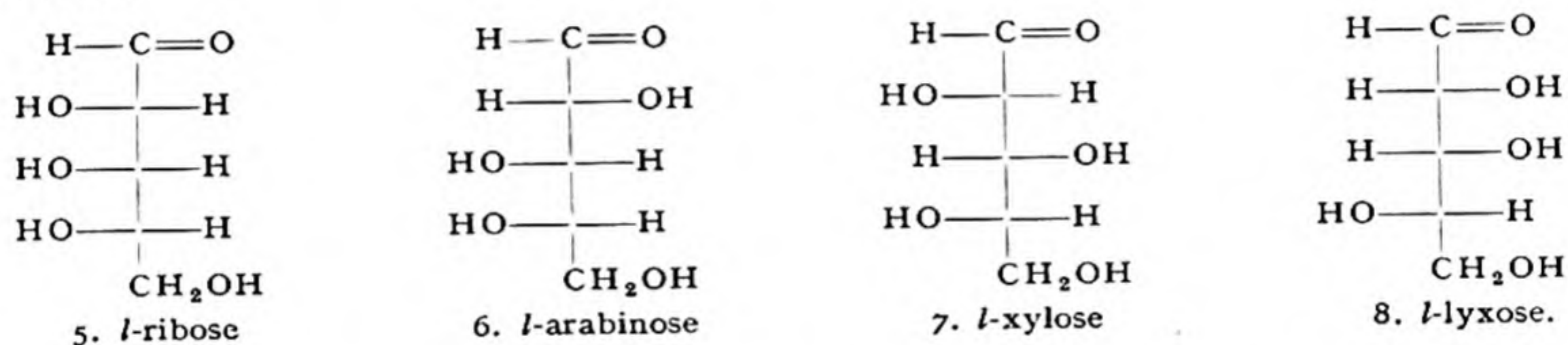
Finally, configuration 1 can be assigned to a laevo-rotatory pentose found as a fission product of the nucleic acids (349), namely, *d*(-)-ribose. Indeed

this sugar gives the same osazone with phenylhydrazine as *d*(—)-arabinose and therefore differs from the latter only in the arrangement of groups around the 2nd carbon atom.

The configuration of *l*(+)-arabinose derived above is confirmed by the fact that this pentose can be degraded to *l*-erythrose, from which *meso*-tartaric acid is produced on oxidation:

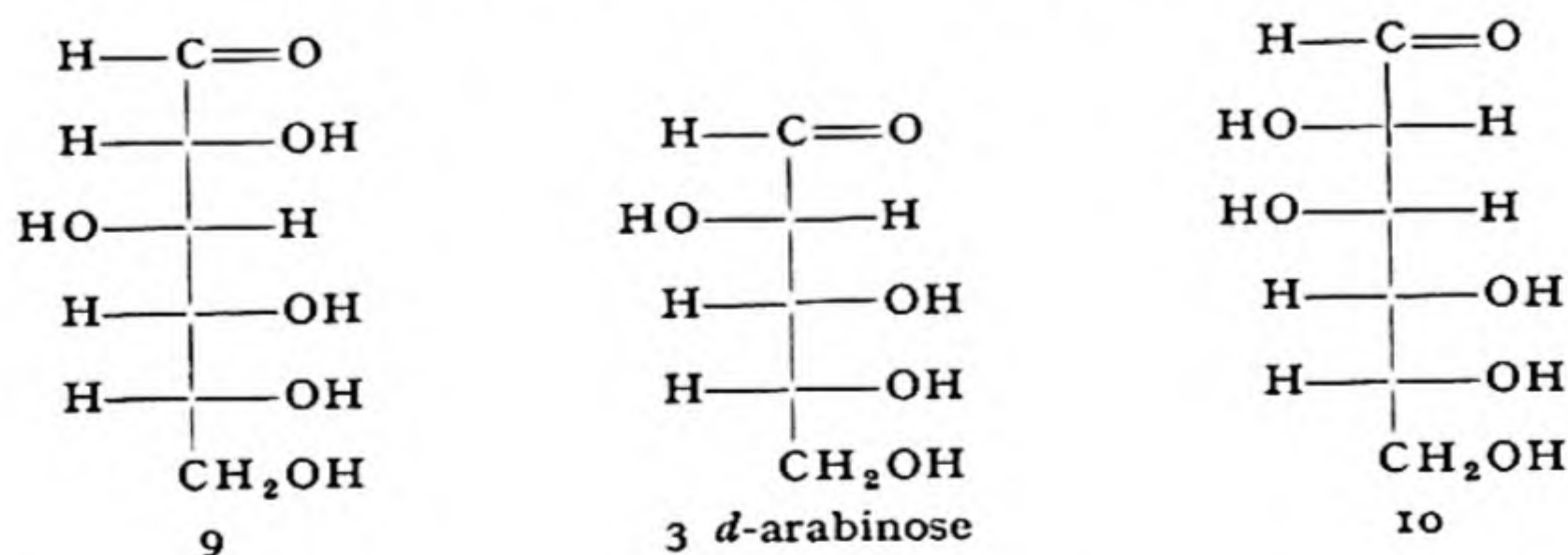


To summarise, the configurations of the pentoses of the *l*-series are as follows:



165. Aldohexoses. The aldehydic formula for a hexose possesses four asymmetric carbon atoms, so that sixteen stereoisomeric aldohexoses can be derived from them; all these are known. The configurations of some of these hexoses are derived in the succeeding paragraphs.

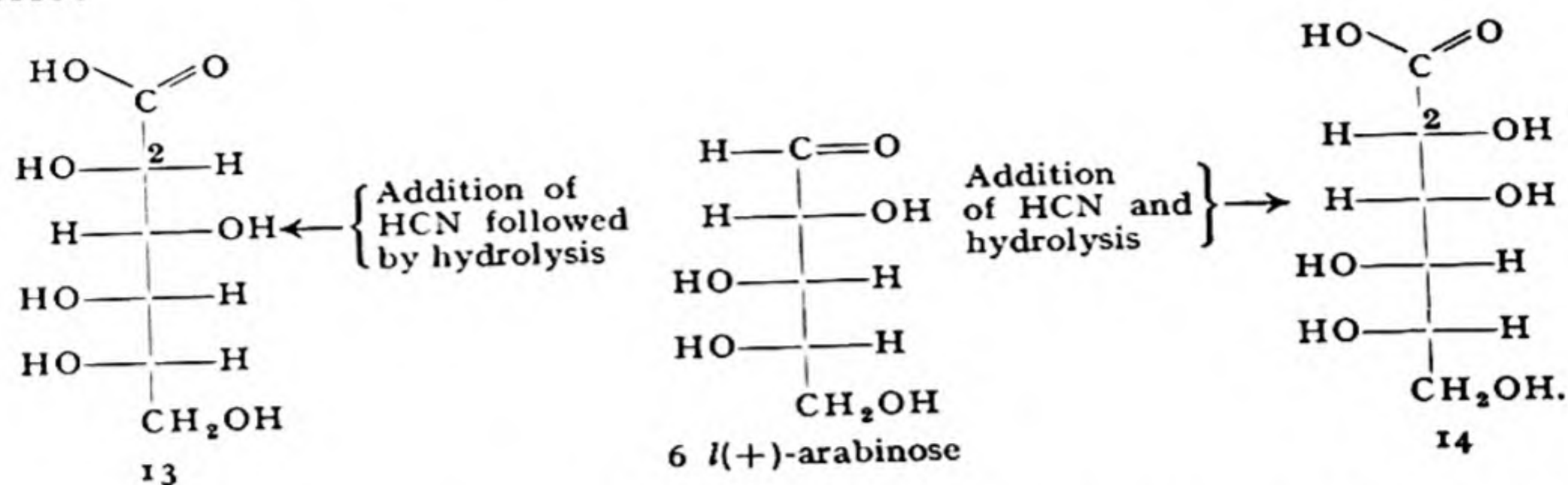
Configuration of glucose and mannose. *d*(—)-Arabinose is obtained by the degradation of naturally occurring dextro-rotatory glucose by one of the methods described in 162. From this it follows that this glucose belongs to the *d*-series and has one of the configurations 9 or 10.



A hexonic acid, *d*-gluconic acid, is produced by oxidising *d*-glucose with

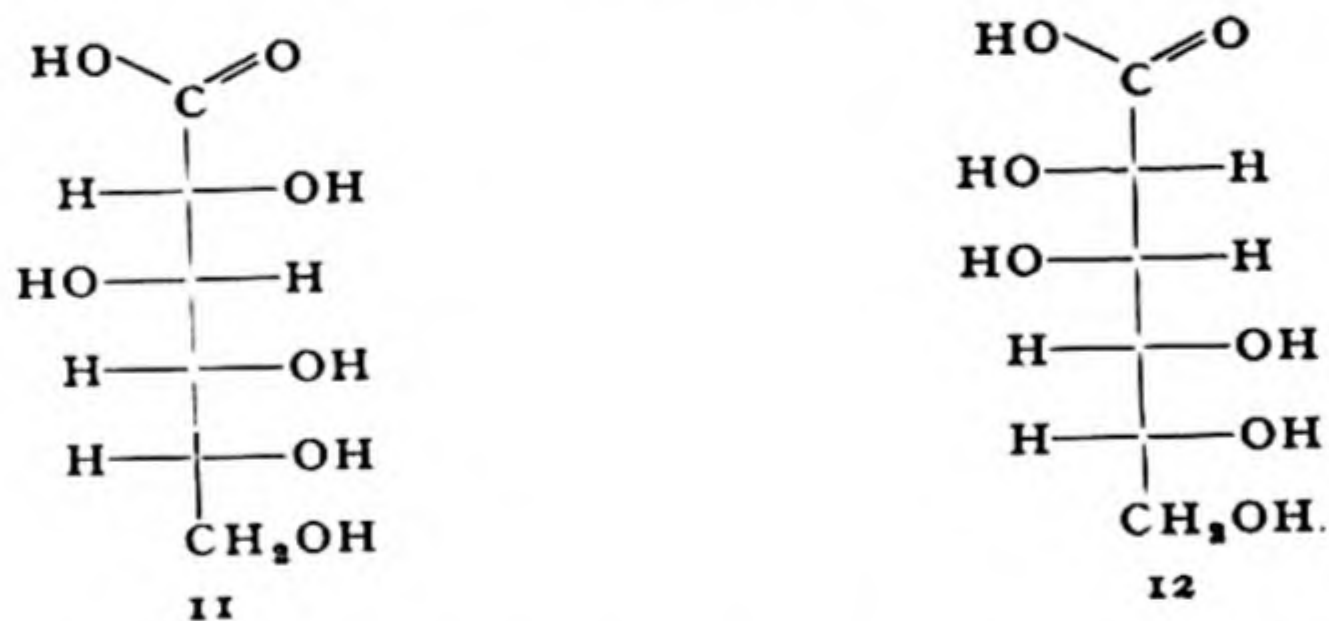
bromine water. From dextro-rotatory mannose, which occurs in plants, and, as will be seen later, which also belongs to the *d*-series, another hexonic acid, namely *d-mannonic acid* is produced.

The optical antipodes of these hexonic acids are obtained from *l*(+)-arabinose by means of the cyanhydrin synthesis; from this it follows that configurations 13 and 14 must be assigned to these hexonic acids of the *l*-series:



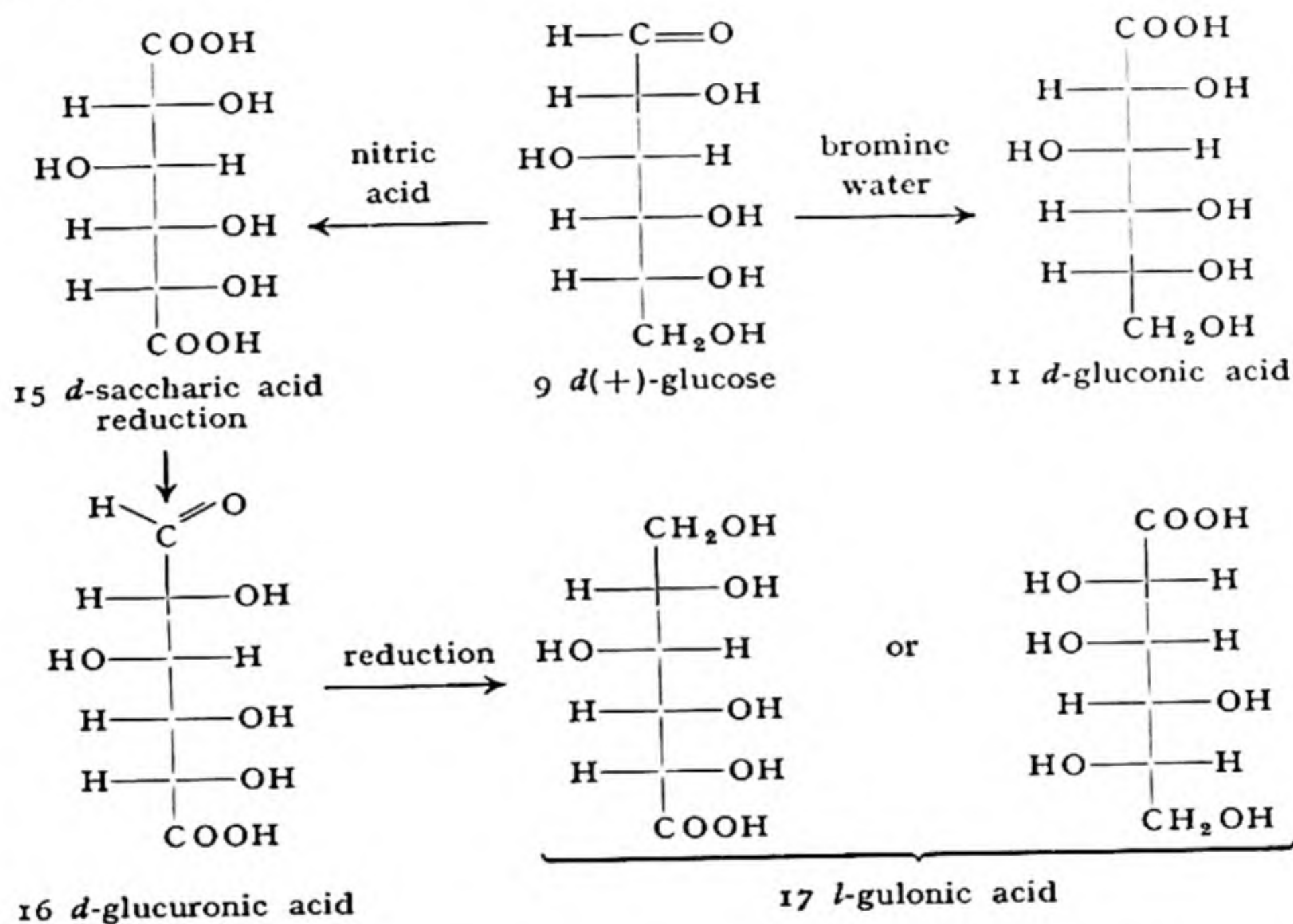
According to this synthesis the hexonic acids of configurations 13 and 14 differ only by the arrangement on carbon atom 2, *i.e.* the carbon atom directly attached to the aldehyde group.

The optical antipodes of these *l*-hexonic acids, *d*-gluconic acid and *d*-mannonic acid mentioned above, can both be obtained by means of the cyanhydrin synthesis from *d*-(—)-arabinose (configuration 3). Hence configurations 11 and 12, which represent the mirror-images of 13 and 14, come into consideration for *d*-gluconic acid and *d*-mannonic acid:



Therefore configurations 9 and 10 must represent *d*-glucose and *d*-mannose. From the following, it is clear that configuration 9 must be assigned to *d*-glucose. A dibasic acid, *d-saccharic acid* (config. 15), is produced when *d*-glucose is oxidised with concentrated nitric acid. This acid can be reduced in the form of a lactone, with sodium amalgam in acid solution, when one of the carboxyl groups is converted into an aldehydic acid; *d-glucuronic acid* (16) is produced.

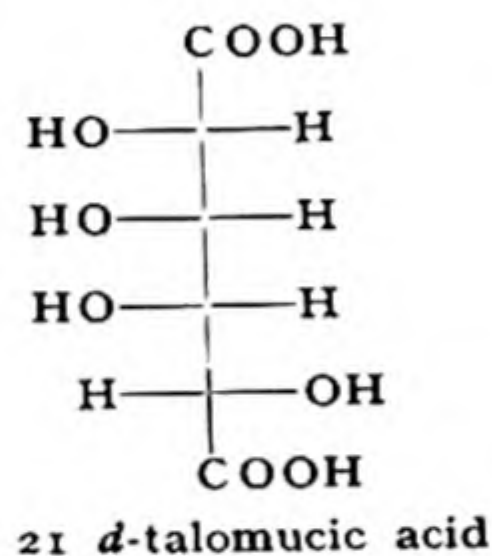
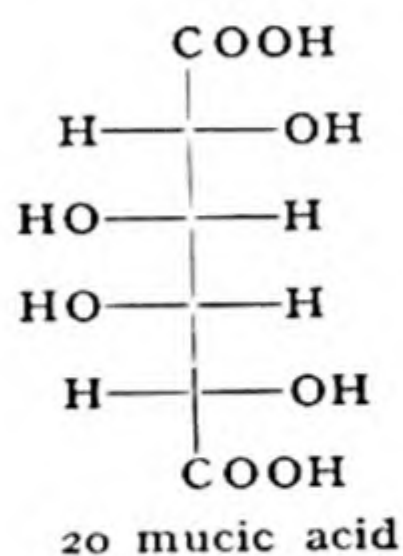
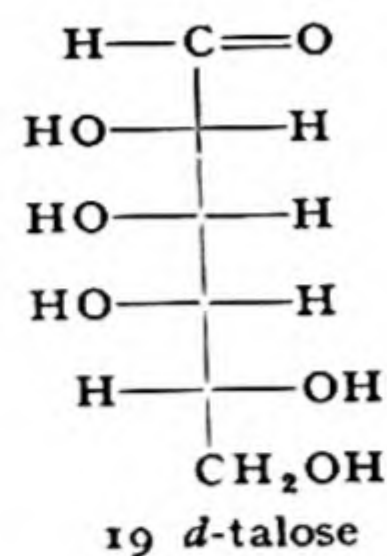
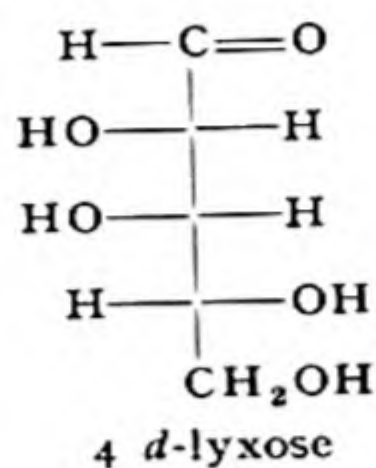
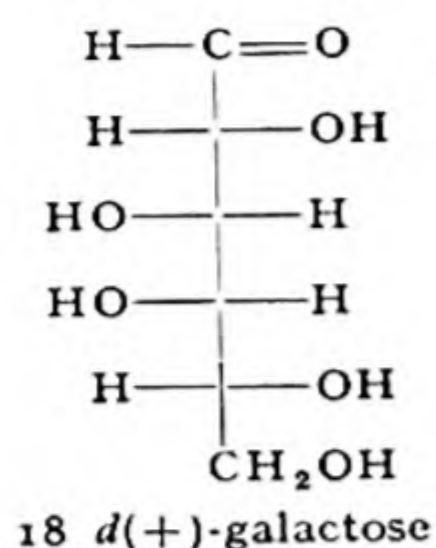
If this reduction is continued, the —CHO group in glucuronic acid is converted into a $\text{—CH}_2\text{OH}$ and a hexonic acid is produced, which is not identical with gluconic acid and is called *gulonic acid*. *d*-Saccharic acid is produced from this gulonic acid (17) by powerful oxidation. Hence *d*-glucose is related to the two stereoisomeric hexonic acids *d*-gluconic acid and gulonic acid. Therefore, configuration 9 must be assigned to *d*-glucose, since two different hexonic acids could not be produced from a hexose having configuration 10.



For the same reason, configuration 10 (page 263) must be assigned to mannose; this sugar is to be designated as *d*(+)-mannose. *d*-Glucose and *d*-mannose differ only in the arrangement about carbon atom 2; since the same osazone is produced from both hexoses by the action of phenylhydrazine, the phenylhydrazine residues in this osazone must be attached to carbon atoms 1 and 2. This has also been proved in some other cases and on this basis it is now assumed that all osazones have a similar structure.

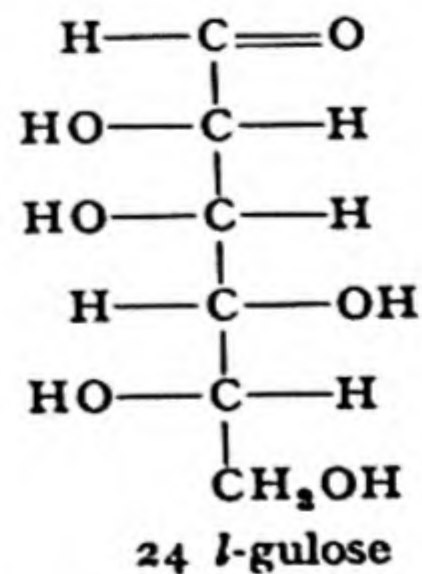
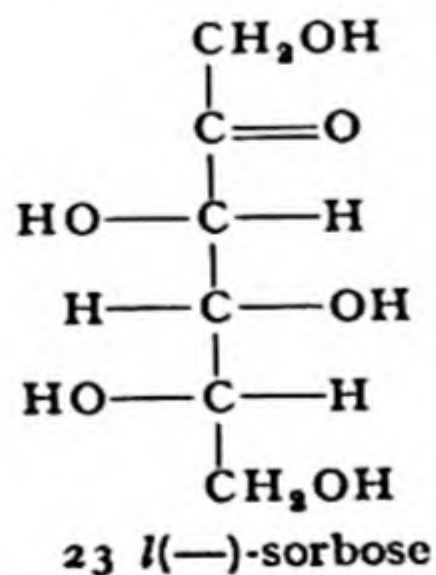
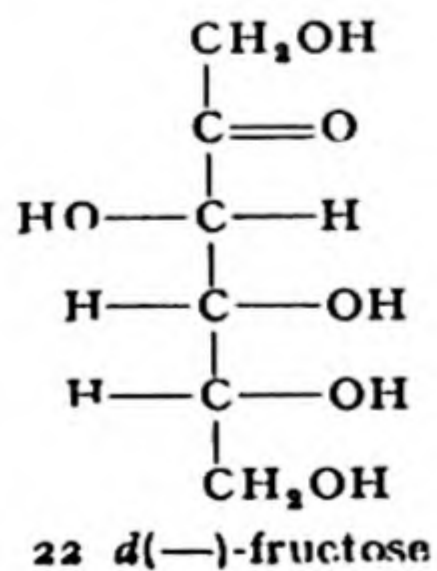
166. Configuration of galactose. *d*-Lyxose is produced by the degradation of dextro-rotatory galactose (163); from this it follows that one of the configurations 18 or 19 must be assigned to *d*-galactose. *Mucic acid*, which is optically inactive and must therefore have configuration 20, since this is identical with its mirror-image, is produced when *d*-galactose is oxidised with nitric acid. From this it follows that *d*-galactose must have configuration 18.

Configuration 19 is assigned to *d*-talose. This sugar, which is not found in nature, gives optically active *talomucic acid* (21) on oxidation. The osazone from *d*-talose is identical with that from *d*-galactose; from this it again follows that the phenylhydrazine residues are attached to carbon atoms 1 and 2.



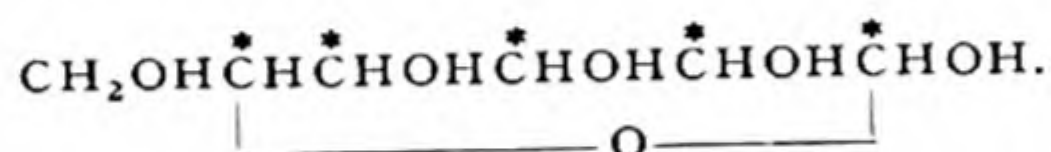
167. Configuration of fructose and sorbose. As was deduced in 161, in fructose the reducing group is attached to carbon atom 2. Since the osazone of naturally occurring laevo-rotatory fructose is identical with the osazones obtained from *d*-glucose and *d*-mannose, configuration 22 is assigned to this fructose; hence laevorotatory fructose belongs to the *d*-series and is to be designated as *d*(—)-fructose.

Laevo-rotatory sorbose (163), a ketose which also carries the reducing group on carbon atom 2, has configuration 23, since it gives the same osazone as gulose (24), an aldose obtained by reduction of the lactone of *l*-gulonic acid (configuration 17 on page 265). Hence laevorotatory sorbose belongs to the *l*-series and is to be designated as *l*(—)-sorbose.



The configurations of the monosaccharides derived above are in agreement with many other reactions of these sugars and their derivatives, so that the stereochemical structures of the compounds in this group may be taken as completely established. These researches, which form an outstanding confirmation of the stereochemical theory of VAN 'T HOFF and LE BEL, are due to E. FISCHER (1852—1919) and his co-workers.

In the above, the aldehydic formula (or the ketonic formula) for the monosaccharides is used as the basis from which projection formulae are derived, which in their turn represent the stereochemical configurations. The reader will be able to convince himself quite easily that the conclusions drawn with regard to the arrangement of the groups around carbon atoms 2—5 (for aldohexoses) or 2—4 (for aldopentoses) remain unchanged when the cyclic acetal formula (160) is introduced in place of the aldehyde formula. According to the cyclic formula however, carbon atom 1 is also asymmetric; the molecule of an aldohexose in the cyclic acetal form contains 5 asymmetric carbon atoms each marked with an asterisk:



According to this formula $2^5 = 32$ stereoisomeric aldohexoses are possible, while only 16 stereoisomers can be derived from the aldehydic formula. *Each of the 16 stereoisomers can however occur in two tautomeric forms, as appears from the following.*

168. Mutarotation; α - and β -forms of the monosaccharides.

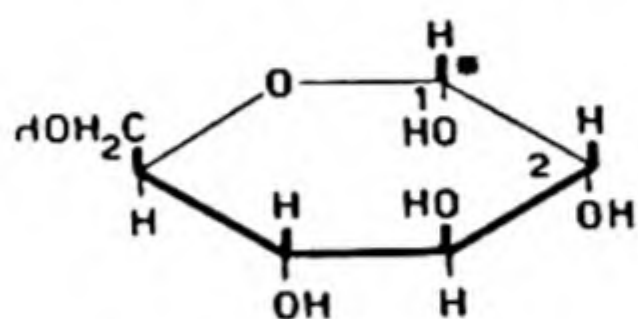
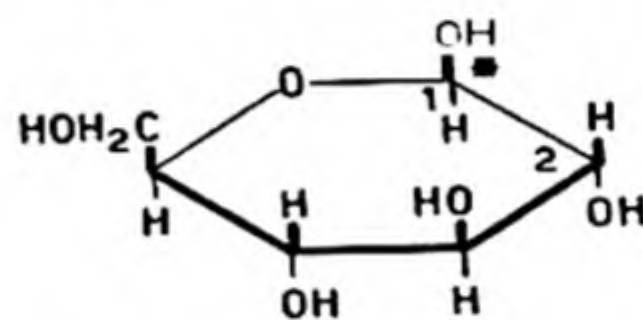
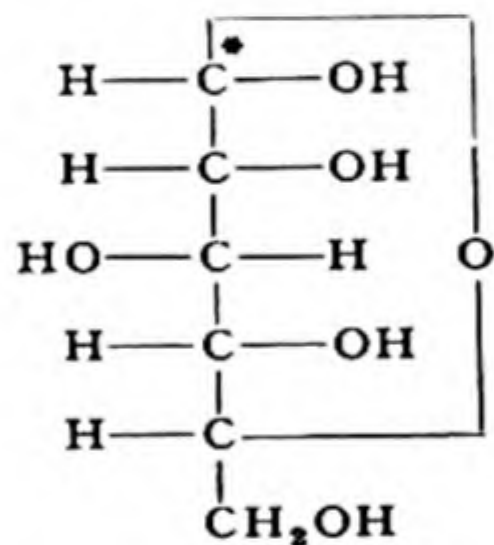
In 1846, long before stereochemical theory had been developed, DUBRUNFAUT discovered, that the rotatory power of a freshly prepared aqueous solution of *d*-glucose rapidly decreases. After some time a value is reached, which remains constant. This phenomenon is called *mutarotation* and is due to the existence of two tautomeric forms of *d*-glucose; these were isolated by TANRET (1905) and designated by him α - and β -glucose.

α -Glucose melts at 146° , has a specific rotation $[\alpha]_D = +109.6^\circ$ and is obtained by evaporating a concentrated aqueous solution at $30-35^\circ$. When a concentrated solution of glucose is heated to $105-110^\circ$ for several hours and cold water and then alcohol is added to the reaction mass, β -glucose crystallises out. The specific rotation of β -glucose is $[\alpha]_D = +20.5^\circ$.

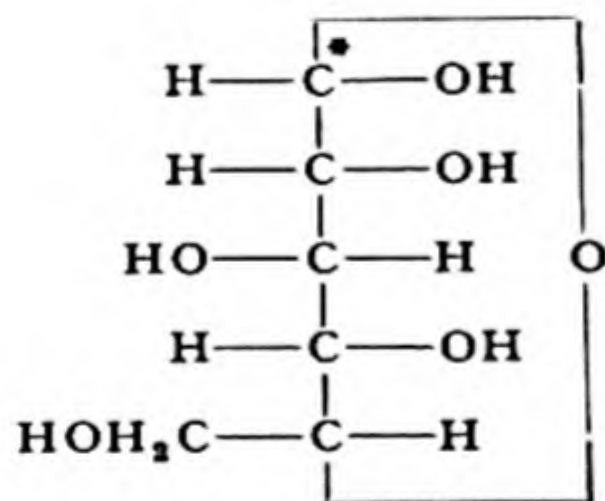
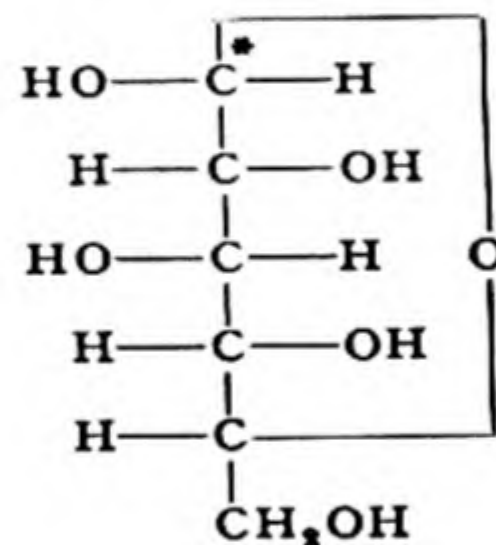
When dissolved in water, α - and β -glucose are converted one into the other until a state of equilibrium is reached, the equilibrium mixture of α - and β -glucose having a specific rotation $[\alpha]_D = +52.3^\circ$. The velocity of this reversible reaction is greatly increased by the presence of small quantities of hydroxyl-ions.

d-Gluconic acid is produced from either α - or β -glucose by gentle oxidation. From this it follows that the arrangement of groups on carbon atoms 2—5 must be the same in both α - and β -glucose. Hence the aldehydic formula takes no account of the existence of α - and β -glucose but this isomerism can be explained by the cyclic formula, since in this, carbon atom 1 is also asymmetric.

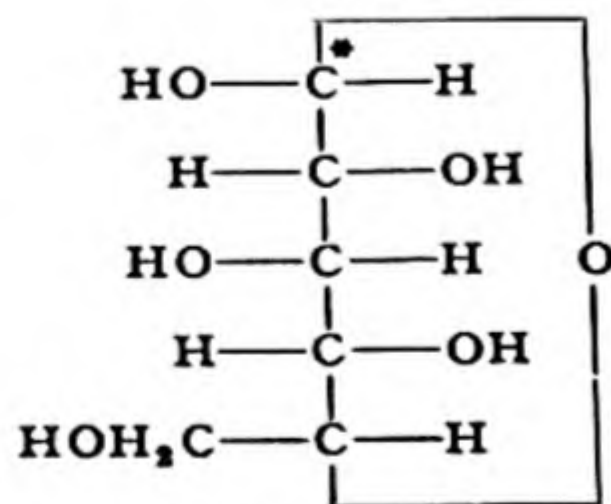
The isomerism between α - and β -glucose is caused by a different arrangement of the hydrogen atom and the hydroxyl-group on carbon atom 1. In the conversion α -glucose \rightleftharpoons β -glucose, this hydroxyl-group and this hydrogen atom change places. Hence this is a case of tautomeric change between stereo-isomers. In the space model of an aldohexose the carbon atoms and the epoxy-oxygen atom, which together form the pyran ring, lie in a flat plane; the hydrogen atoms and hydroxyl groups on carbon atoms 1 to 4 lie above and below this plane. In the space figures below and in the corresponding projection formulae the carbon atoms of the active group are marked by an asterisk.

Fig. 47. α -glucoseFig. 48. β -glucose

or

projection formulae
for *d*- α -glucose.

or

projection formulae
for *d*- β -glucose.

According to these models, in α -glucose the two hydroxyl groups on carbon atoms 1 and 2 lie on the same side of the plane of the ring. β -Glucose

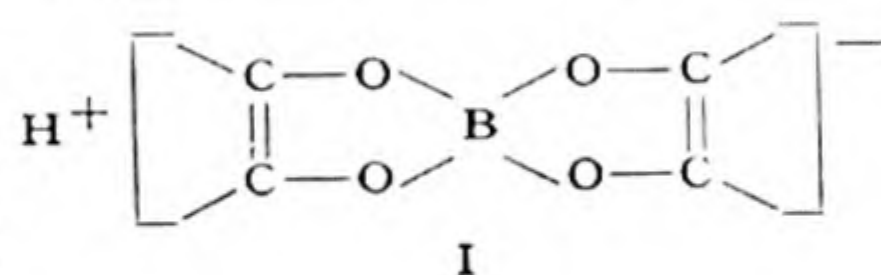
differs from α -glucose in the position of the hydroxyl group on carbon atom 1. In β -glucose the hydroxyl groups attached to carbon atoms in the plane of the ring lie alternately on either side of this plane.

This has been shown by BÖESEKEN by means of a method depending on the effect of compounds with two or more hydroxyl groups on the electrical conductivity of boric acid.

A 0.5-normal solution of boric acid has a conductivity of 25×10^{-6} (in Kohlrausch units), and a 0.5-normal solution of *o*-dihydroxybenzene (catechol; 232) one of 14×10^{-6} . For a solution which is 0.5-normal with regard to both boric acid and catechol, the conductivity is 555×10^{-6} . Thus the conductivity of boric acid increases considerably on adding catechol. The conductivity of a 0.5-normal solution of resorcinol (*m*-dihydroxybenzene; 232) is 6×10^{-6} and that of a solution containing boric acid and resorcinol, both at the same normality, is 25×10^{-6} . Hence in this case there is no question of an increase in the conductivity of boric acid and neither is there on the addition of *p*-dihydroxybenzene (quinol). When 1,2,3-trihydroxybenzene (pyrogallol; 232) in which the three hydroxyl groups are attached to adjacent carbon atoms, is added to boric acid solution, the conductivity increases considerably.

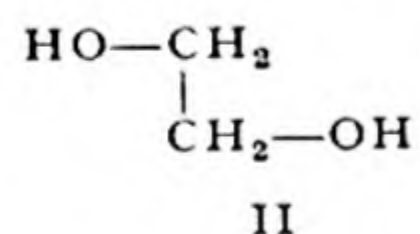
The increase in the conductivity is not caused however by any compound in which two hydroxyl groups occur on adjacent carbon atoms, for glycol (110) causes no such increase. The hydroxyl groups in the polyhydric phenols (232) are situated in the same plane as the carbon atoms in the benzene ring. Consequently, a complex acid of the type I

can be formed from catechol and boric acid and this compound is very much more strongly ionised than boric acid itself; in the complex anion the boron atom is attached to four oxygen atoms derived from the hydroxyl groups in two molecules of catechol. In some cases it is possible to isolate such compounds.



Similar compounds from *m*- or *p*-dihydroxybenzene and boric acid cannot be produced because the bonding forces between C and the OH-group would have to be bent too far from their original directions.

Hence it must be assumed that in the glycol molecule the OH-groups are separated as far as possible from each other by mutual repulsion (II).



The conductivity of boric acid is increased by adding glycerol, erythritol, mannitol, dulcitol and sorbitol. Therefore in these compounds at least two hydroxyl groups must lie near one another in the space model. Hence in the change in the conductivity of boric acid by polyhydric alcohols we have a means of determining the positions of the hydroxyl groups in the space models of these compounds.

BÖESEKEN found that on adding α -glucose to boric acid the conductivity increased but then slowly decreased until a constant final value was reached. This occurs because α -glucose is slowly converted into β -glucose. When β -glucose is added to boric acid the conductivity again increases but increases still further with the time since β -glucose slowly changes into α -glucose. It is assumed therefore that in α -glucose two hydroxyl groups stand in a corresponding position, *i.e.* that they lie on the same side of the plane of the ring.

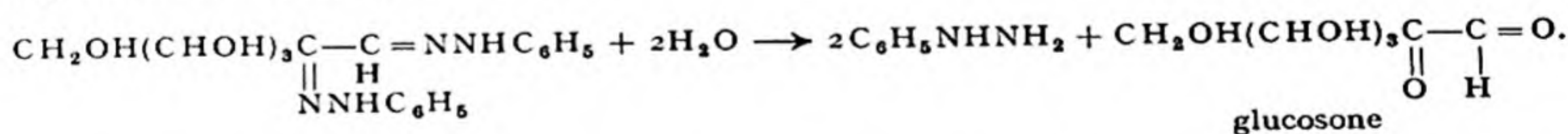
From the structural formula for methylglucosides given in 160, it follows that for these compounds also, two stereoisomeric forms are possible, differing in the arrangement of the CH_3O -group and the H-atom on the first carbon atom. Both isomers are known. By the action of methanol and a little hydrogen chloride on glucose there is produced mainly a methylglucoside with a specific rotation $[\alpha]_D = +157.5^\circ$ together with a small quantity of an isomer with a specific rotation of $[\alpha]_D = -32^\circ$.

These methylglucosides do not change into one another when dissolved in water; however, when they are dissolved in alcohol, to which a small amount of hydrogen chloride is added as a catalyst, a slow reversible reaction occurs. The behaviour of the methylglucosides towards enzymes (208) is noteworthy. The methylglucoside with $[\alpha]_D = +157.5^\circ$ is split up into methanol and glucose by the enzyme *maltase*. The solution shows a decreasing mutarotation hence the glucose is present in the α -configuration. Therefore the α -configuration is assigned to this methylglucoside. The methylglucoside with $[\alpha]_D = -32^\circ$ is not broken down by maltase but by *emulsinase* (179, 208). The solution shows an increasing mutarotation and therefore contains β -glucose. Hence this methylglucoside has the β -configuration.

The phenomenon of mutarotation occurs with all monosaccharides and with those disaccharides which contain a reducing group. In some cases it has been possible to isolate the α - and β -forms. Thus a particular hexose may occur in four stereoisomeric forms, e.g. *d*- α -glucose, *d*- β -glucose, *l*- α -glucose and *l*- β -glucose.

Conversion of hexoses into isomeric sugars

169. By warming osazones gently with concentrated hydrochloric acid, two molecules of phenylhydrazine are split off with the formation of compounds containing an aldehydo and a keto-group and called *osones*. *Glucosone* is produced from glucosazone:



By treatment with zinc dust and acetic acid, the terminal group of the osone is reduced; thus fructose $\text{CH}_2\text{OH}(\text{CHOH})_3\text{COCH}_2\text{OH}$ is produced from glucosone.

By this method, discovered by E. FISCHER, aldoses can be converted into ketoses; the fructose obtained in this manner from *d*-glucose, is identical with fructose occurring in nature.

The conversion of a ketose into an aldose may be carried out as follows. By the reduction of fructose, two stereoisomeric hexitols are produced,

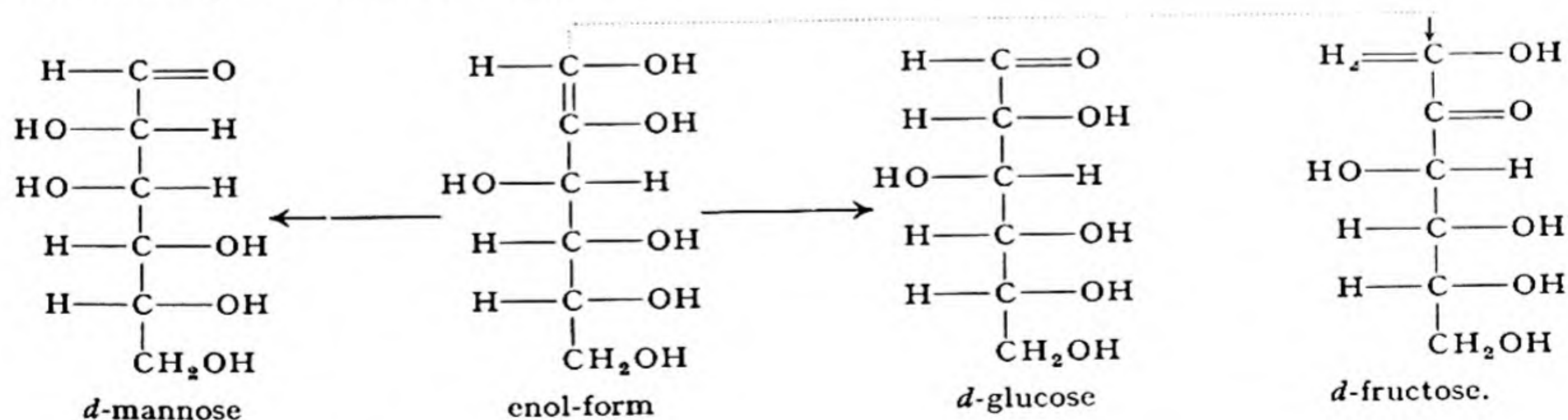
sorbitol and mannitol which can be separated by a difference in solubilities. *d*-Mannonic acid is produced by the oxidation of *d*-mannitol and the lactone of this acid can be reduced to *d*-mannose with sodium amalgam.

On heating an aqueous solution containing some quinoline or pyridine, *d*-mannonic acid is partially converted into *d*-gluconic acid. Conversely, *d*-gluconic acid may also be converted into *d*-mannonic acid. In these reversible conversions the OH and H on the second carbon atom change places.

Thus by means of this reaction *d*-glucose can be obtained from *d*-mannose and vice versa. Similar conversions of hexonic acids have been observed also in other cases, and it is always found that an interchange of H and OH occurs only on the carbon atom situated next to the carboxyl group.

E. FISCHER has made use of these reactions for the *synthesis of a number of monosaccharides*. In 162 it was mentioned that a mixture of hexoses is produced by condensation of formaldehyde or glyceraldehyde, from which the osazone of *dl*-fructose can be obtained. From this the osone can be prepared and converted into *dl*-fructose. By reduction of *dl*-fructose, *dl*-mannitol is obtained and from the latter, *dl*-mannonic acid by oxidation. This *dl*-mannonic acid is resolved into its *d*- and *l*-components by means of the strychnine salts, from which *d*- and *l*-mannose are prepared; *d*- and *l*-mannonic acids can be converted into *d*- and *l*-gluconic acids from which *d*-glucose and *l*-glucose can be obtained.

d-Glucose, *d*-mannose and *d*-fructose are converted reversibly into one another in weakly alkaline aqueous solution (LOBRY DE BRUYN and ALBARDA VAN EKENSTEIN). In order to explain this interconversion, it is assumed that in alkaline solutions an enol-form of these monosaccharides is produced, from which the three isomeric sugars may be produced by conversion into the aldehyde or keto-forms:



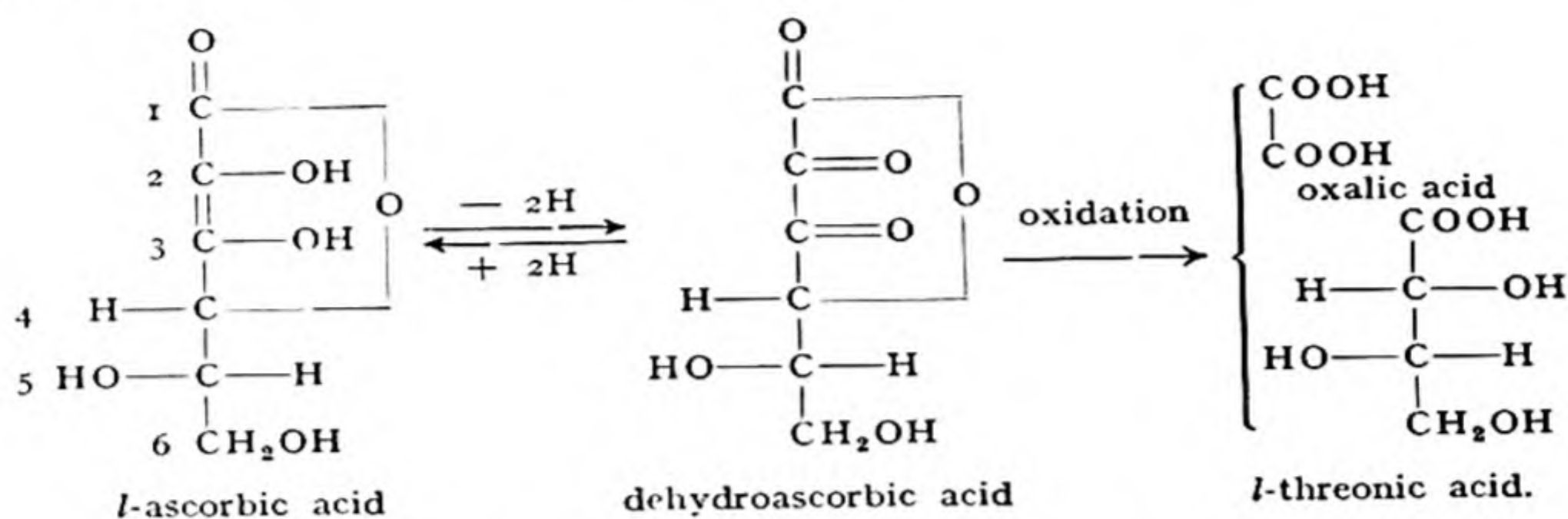
Some derivatives of the hexoses

170. *d*-Glucuronic acid (for configuration see formula 16 on page 265) in the free state forms a viscous liquid but the lactone has been obtained crystalline. Derivatives of glucuronic acid, *e.g.* *phenylglucuronic acid*, which is derived from glucuronic acid

by replacing the OH-group of the reducing group by OC_6H_5 , sometimes occur in very small quantities in human urine.

l-Ascorbic acid or vitamin-C (see 306), $\text{C}_6\text{H}_8\text{O}_6$, is a well defined crystalline substance, soluble in water, which melts with decomposition at $189\text{--}190^\circ$ and is optically active: $[\alpha]_D = +49^\circ$.

The structure of this important compound, which was established (1933) mainly by HIRST and his co-workers, will be explained by means of the formulae below:



Ascorbic acid is converted by gentle oxidising agents into *dehydroascorbic acid*, which can be reduced again into ascorbic acid. By further oxidative degradation oxalic acid and *l-threonic acid*, *i.e.* the acid formed by careful oxidation of *l-threose*, are produced.

Ascorbic acid has the properties of a mono-basic acid, in the sodium salt one hydrogen atom is replaced by sodium. The acid properties must be ascribed to the presence of two enolic hydroxyl groups, *i.e.* to the hydroxyl groups attached to the carbon atoms of the group $>\text{C}=\text{C}<$. The primary oxidation product of ascorbic acid, incorrectly called dehydro-ascorbic acid, has no acid properties and shows the characteristics of a lactone.

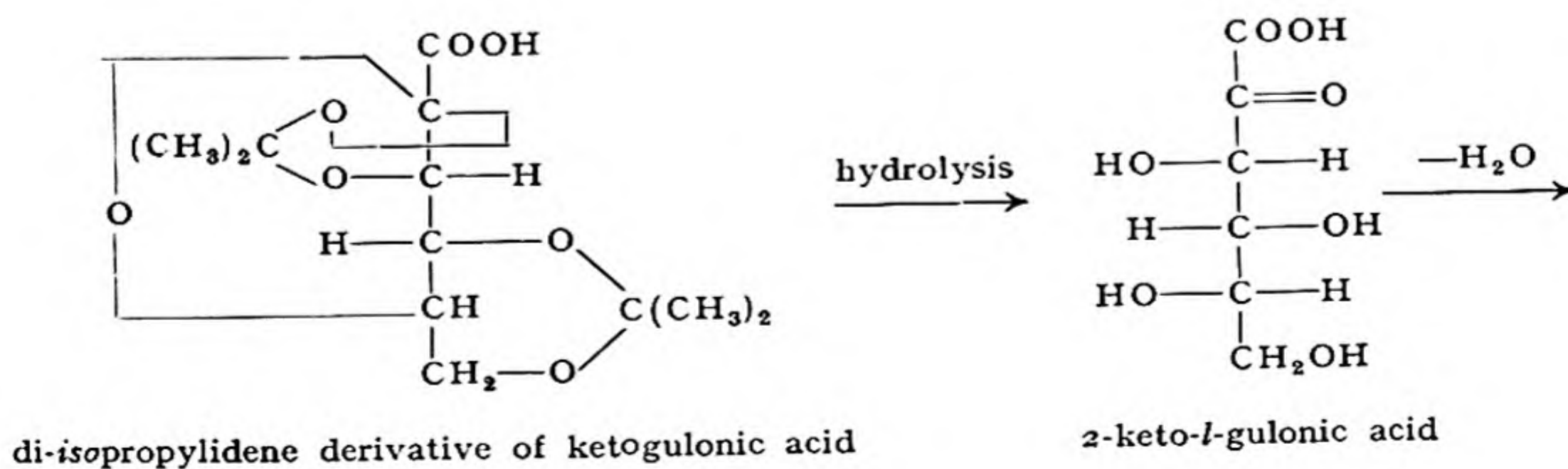
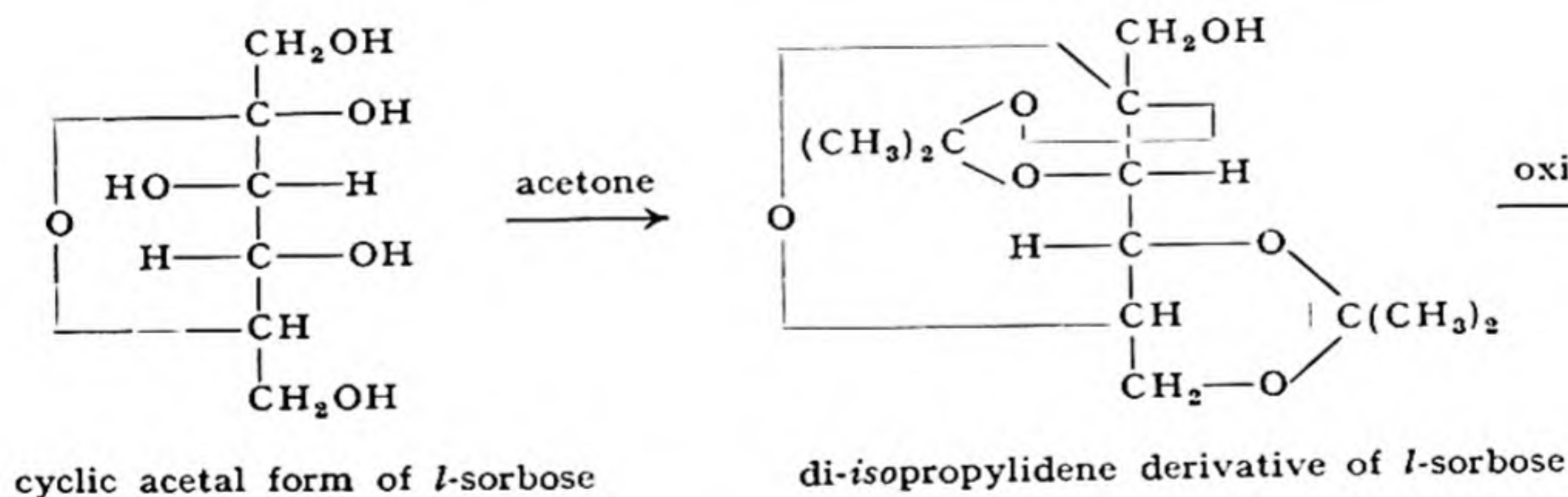
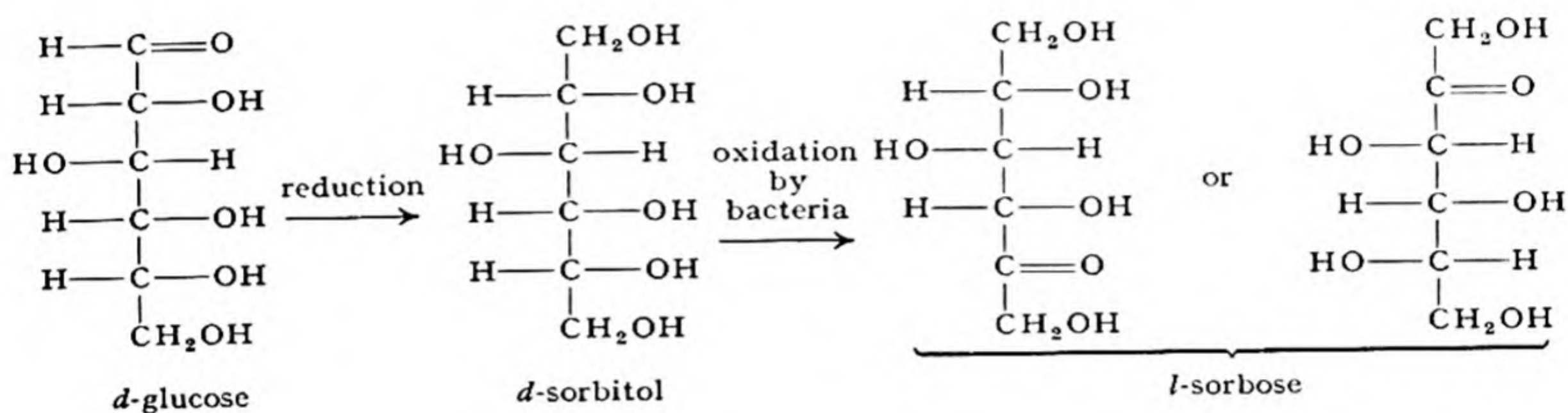
By the action of diazomethane on ascorbic acid, a dimethyl ether is produced, in which both hydrogen atoms of the enol-groups are replaced by methyl. This compound is neutral in character and reacts with one molecule of acetone to form an *isopropylidene* derivative. From this it follows, that in the dimethyl ether two hydroxyl groups (5 and 6) are present on adjacent carbon atoms.

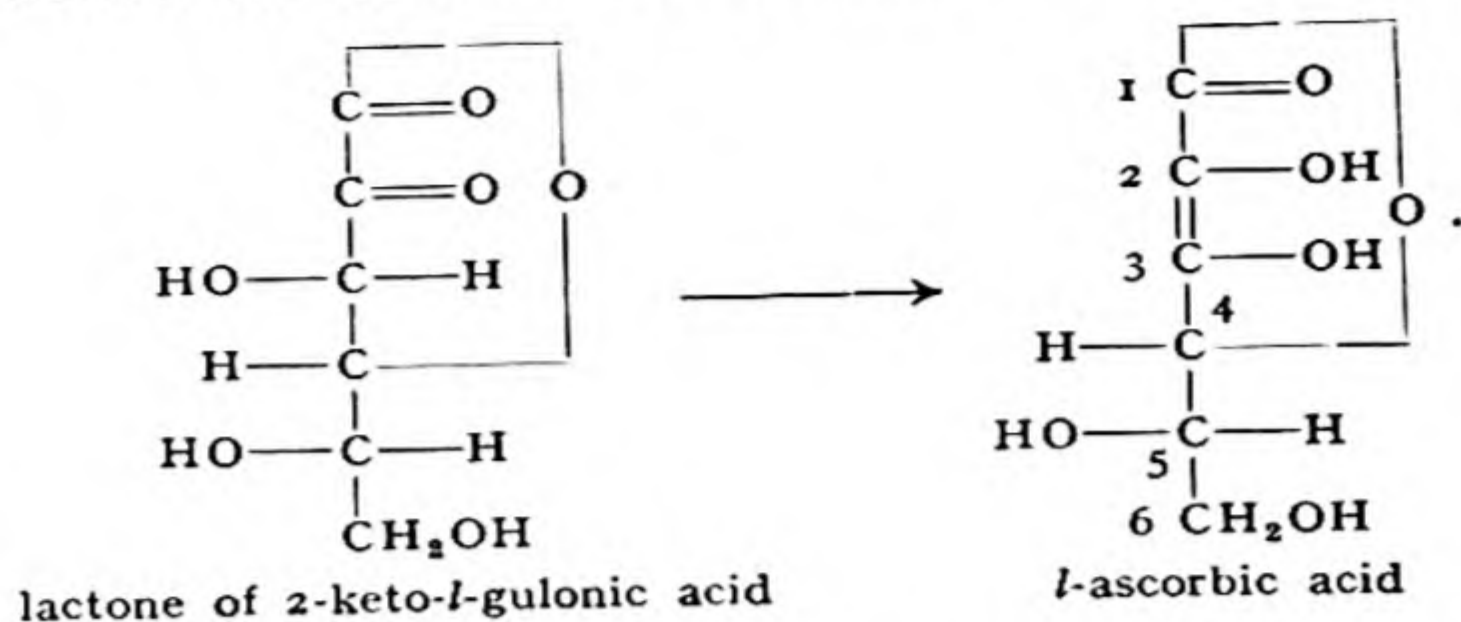
The peculiar properties of ascorbic acid are caused by the atomic grouping I, which is known as the *enediol-group*. This grouping easily gives up two hydrogen atoms and is thereby converted into II:



Ascorbic acid has powerful reducing properties and is an example of a stable aliphatic compound in which two hydroxyl groups attached to doubly bound carbon atoms occur.

d-Glucose is the starting material for the preparation of *l*-ascorbic acid on a commercial scale; it is first of all reduced catalytically under pressure to *d*-sorbitol from which *l*-sorbitol is obtained by the action of sorbose bacteria. The *l*-sorbitol is converted into a di-isopropylidene-derivative by treatment with acetone and a condensing agent, which is oxidised to the di-isopropylidene derivative of 2-ketogulonic acid; the isopropylidene-residues are then split off by the action of dilute acids with the formation of 2-ketogulonic acid, which passes over into the lactone. This lactone — the tautomeric form of ascorbic acid — can be converted into the latter by warming with dilute acids:

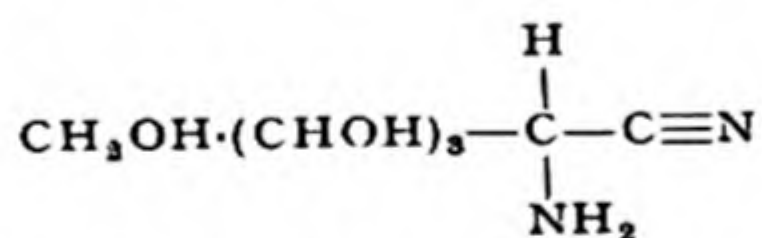




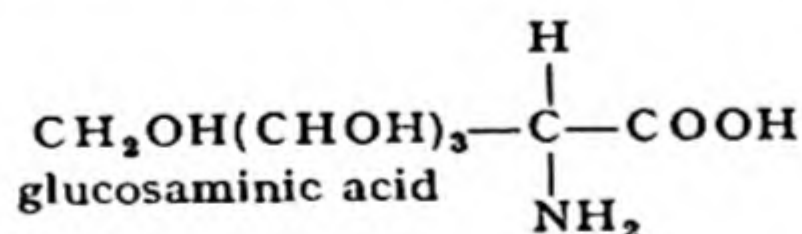
It is very remarkable that the optical antipode of *l*-ascorbic acid, viz. *d*-ascorbic acid—which was prepared by REICHSTEIN by another synthetic method—is physiologically inactive.

171. *Glucosamine*, $\text{C}_6\text{H}_{13}\text{O}_5\text{N}$, is produced from *chitin* by warming it with strong hydrochloric acid (LEDDERHOSE, 1876); in this way an equivalent quantity of acetic acid is produced along with glucosamine. Chitin is a constituent of the bodies of insects and the protective covering of crustaceae (shell-fish) and can be prepared from lobster or shrimp shells: it also occurs in the vegetable kingdom, *e.g.* in the cell walls of fungi (*Agaric*).

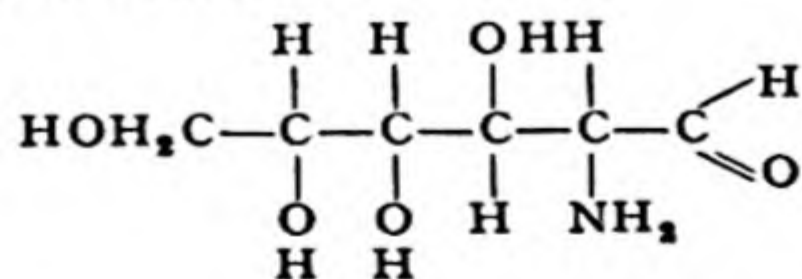
Glucosamine has reducing properties, is optically active, gives a well defined crystalline salt with hydrochloric acid and so contains a basic group present in the form of an amino-group since nitrogen is evolved by the action of nitrous acid. *d*-Glucosazone is produced by warming glucosamine hydrochloride with phenylhydrazine: apparently in this reaction, the NH_2 -group present in glucosamine is split off, probably in the form of ammonia. These and other observations indicate that glucosamine must be regarded as an *aminohexose*, *i.e.* as a derivative of an aldohexose in which one of the alcoholic hydroxyl-groups is replaced by an amino-group. This opinion has been completely established by a synthesis of *d*-glucosamine carried out by FISCHER and LEUCHS. By the action of ammonia and hydrogen cyanide on *d*-arabinose (compare the method of STRECKER for the synthesis of *l*-amino-acids, 194) a compound having the following structure



is obtained, from which hydrolytic fission by means of hydrochloric acid produces a hydroxyamino-acid, which is identical with *glucosaminic acid*, obtained by the oxidation of glucosamine:



The configuration of glucosamine has been established as 2-amino-*d*-glucose by a recent synthesis of W. N. HAWORTH:



Glucosamine and *chondrosamine* (2-amino-*d*-galactose) are found as fission products of mucoproteins (201).

By hydrolysing chitin under certain conditions, the acetyl derivative of glucosamine, in which the acetyl group is probably attached to nitrogen, may be obtained.

It is assumed that chitin is built up from acetylglucosamine-residues in the same way as cellulose is built up from glucose-residues (187).

(b) *Disaccharides*

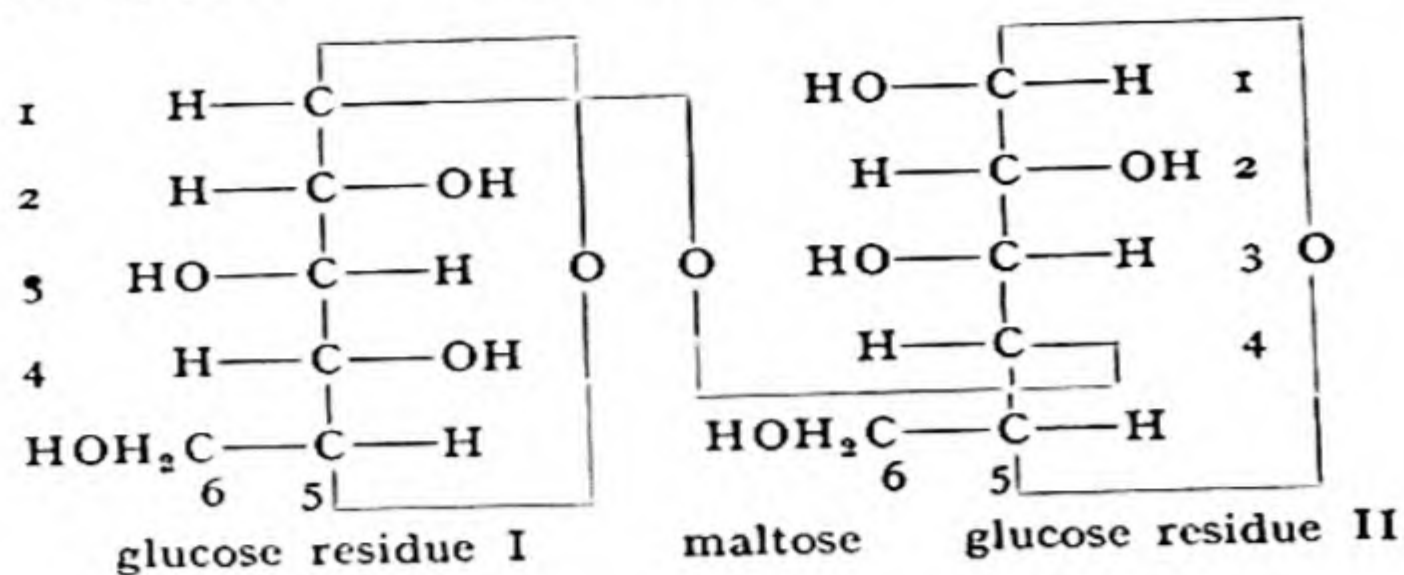
172. Most disaccharides are built up from hexose residues and have the formula $C_{12}H_{22}O_{11}$, derived from $2C_6H_{12}O_6 - H_2O$. Either one or two different hexoses are produced by the hydrolysis of the hexodisaccharides by boiling with dilute acids or by the action of enzymes (208). Since this hydrolytic fission takes place very easily, it is assumed that the hexose residues are joined together in the disaccharides through an oxygen atom.

A few disaccharides are known which are built up from a hexose and a pentose. A glucoside occurs in the seeds of the vetch (*Vicia angustifolia*) which may be split up into hydrocyanic acid, benzaldehyde and a disaccharide, *vicianose*, which gives *d*-glucose and *l*-arabinose on hydrolysis. A glucoside, *apiin* (a more correct name would be *apioside*) occurs in parsley which gives a disaccharide when treated with acids giving glucose and *apiose* (163) on further hydrolysis.

173. Maltose. This disaccharide, which was discovered by DUBRUNFAUT in 1847, crystallises in fine colourless needles and in this form has the formula $C_{12}H_{22}O_{11}H_2O$ and is strongly dextrorotatory. It is produced from starch by the action of *diastase* (31) and is an important intermediate product for the fermentation industries. *d*-Glucose is the sole product formed by boiling maltose with dilute mineral acids.

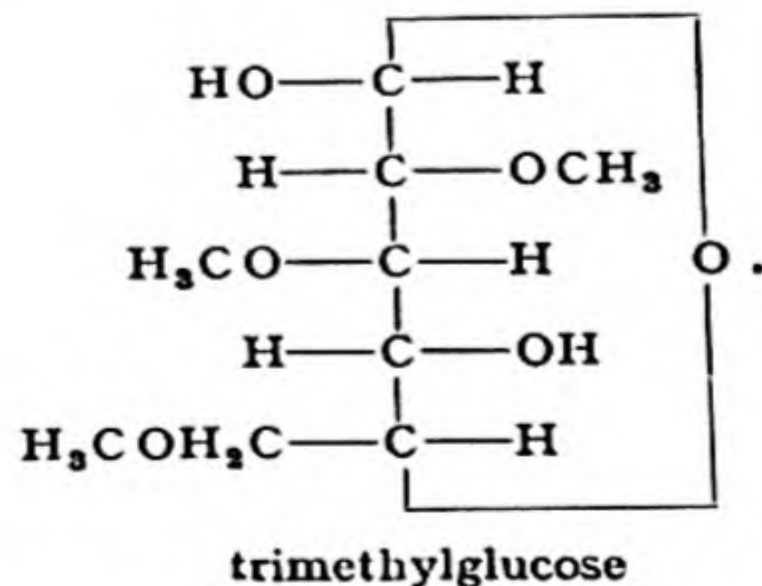
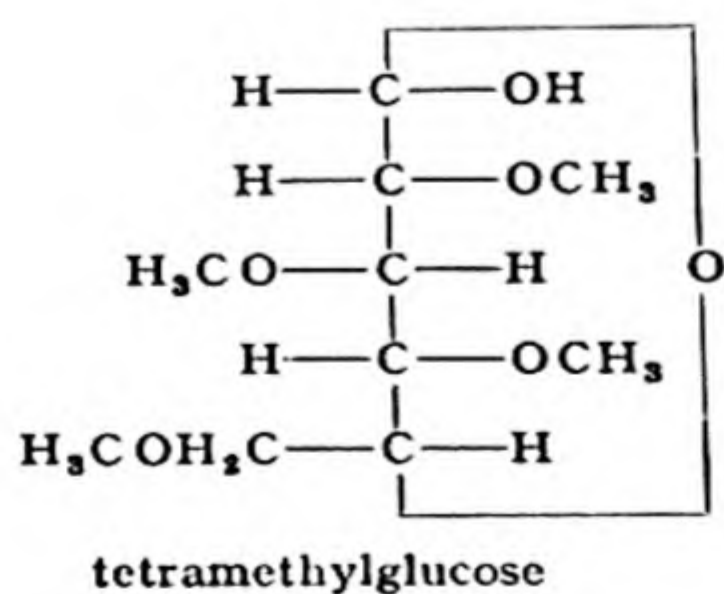
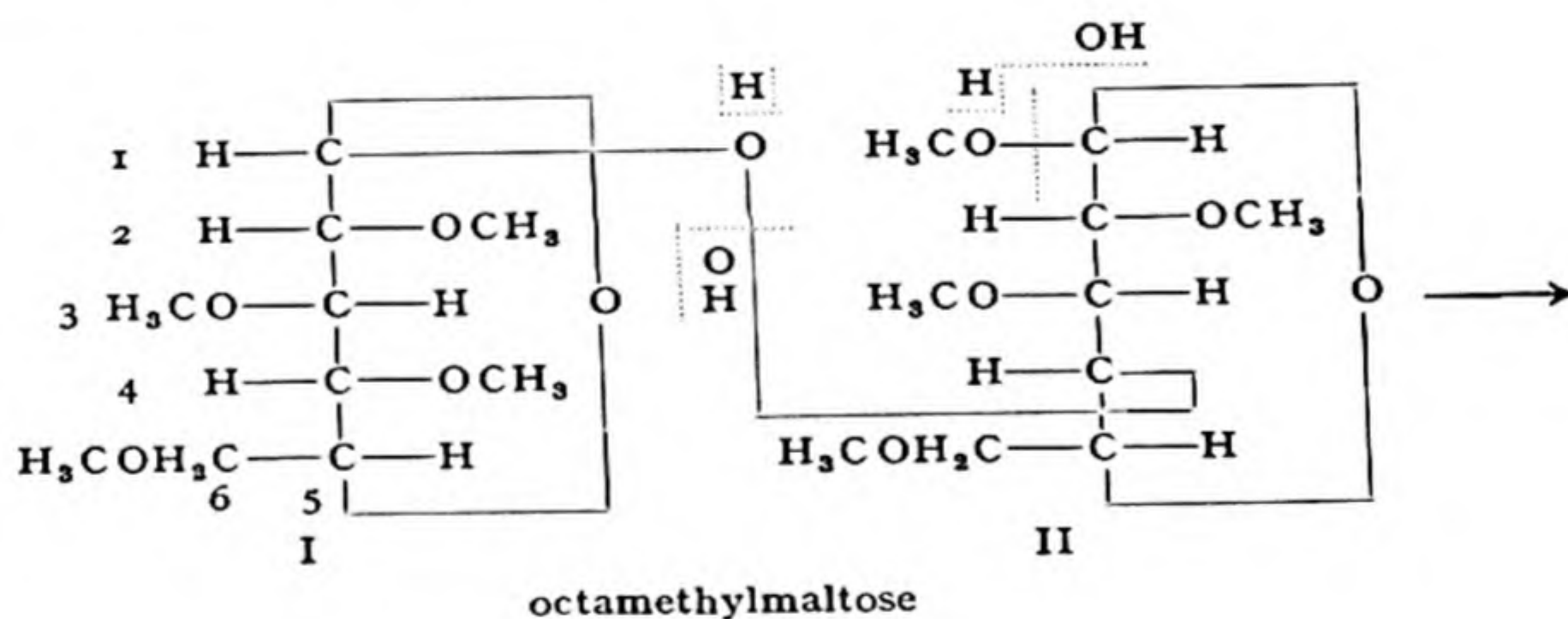
Maltose shows the reactions of the monosaccharides. It reduces an alkaline copper solution and forms an osazone called *maltozone*. On oxidation, a monobasic acid, *maltoibionic acid* $C_{12}H_{22}O_{12}$, is produced, which gives *d*-gluconic acid, $CH_2OH(CHOH)_4COOH$, on hydrolytic fission. From the above, it follows that of the two active groups present in two molecules of *d*-glucose, only one remains in maltose, for no dibasic acid is formed on oxidation and the osazone of maltose contains two and not four phenylhydrazine residues.

Hence the two molecules of *d*-glucose must be joined in such a way that the oxygen in only one of the active groups is involved, which is expressed by the following structural formula:



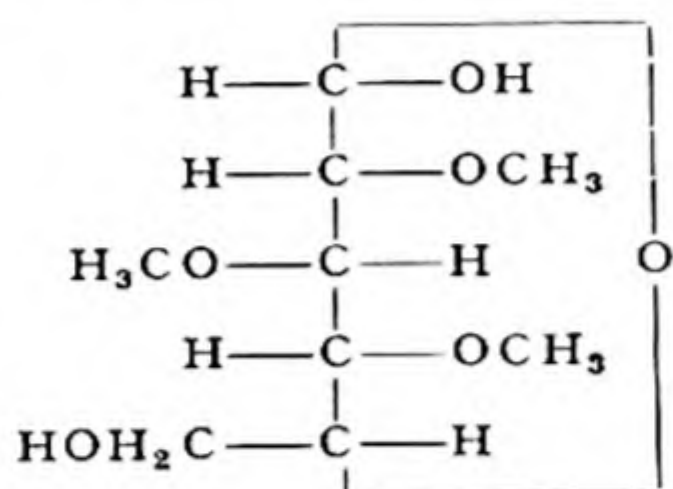
Since only one reactive group is present in the molecule, the first carbon atom in glucose residue I must be joined through an oxygen atom to one of the carbon atoms 2, 3, 4 or 6 in the second glucose residue II.

It has been proved by IRVINE and HAWORTH that the oxygen bond in the maltose molecule is situated between carbon atoms I_1 and II_4 . In their method of determining structure, which has been successfully applied to the examination of other disaccharides and several polysaccharides, these investigators employ the methylation method which they originated. (compare 160). The hydrogen atoms in all the eight hydroxyl groups in maltose can be replaced by methyl groups by methylation. This octamethyl-derivative is hydrolysed by heating with dilute hydrochloric acid with the production of a mixture of tetra- and tri-methylglucose, which can be resolved into its components by making use of the difference in solubility in chloroform:

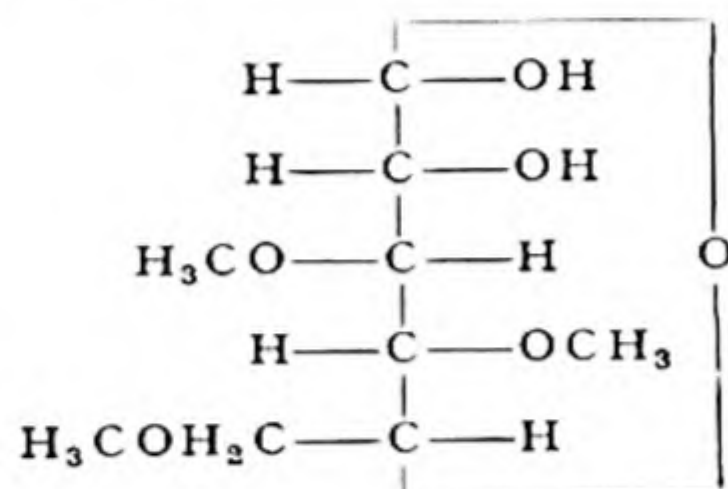


Tetramethylglucose is identical with the methylation product of glucose (160). The trimethylglucose is derived from residue II so that the alcoholic hydroxyl group in this molecule is produced during the hydrolysis. Therefore, if it can be determined which carbon atom carries this hydroxyl group, the position of the oxygen bridge between the hexose residues in maltose is established.

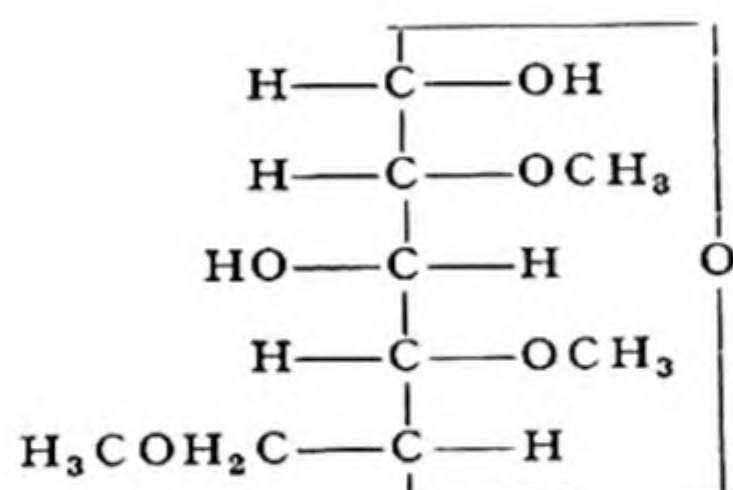
Ignoring the occurrence of α - and β -forms, four isomers are possible for a trimethylglucose with a free reactive group:



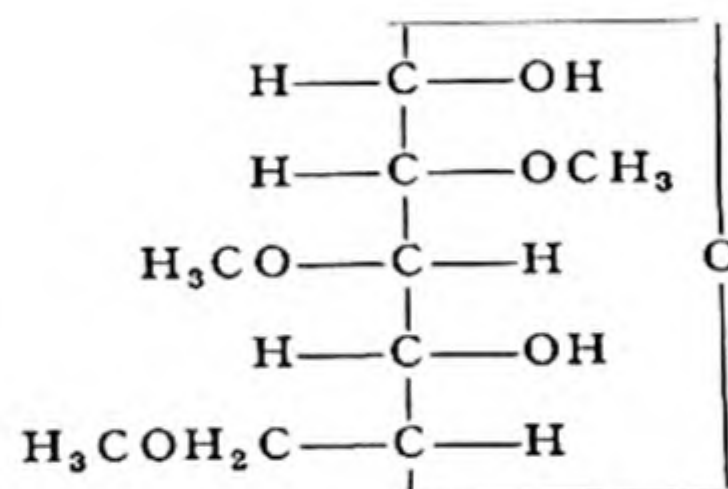
I.



II.

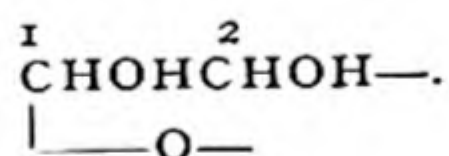


III.



IV.

Since the trimethylglucose obtained from maltose fails to give an osazone, formula II is excluded, because a compound with this structure should form an osazone on account of the presence of the grouping:



From the following facts it may be concluded that the trimethylglucose from maltose has structure IV (2,3,6-trimethylglucose). On oxidation with nitric acid there is produced a *dimethylsaccharic acid*; i.e. a dibasic acid with a chain of six carbon atoms. From this it follows that one methyl group, which is removed by oxidation, must be attached to carbon atom 6. When the trimethylglucose is oxidised with very concentrated nitric acid, more extensive degradation occurs with the formation of dimethyltartaric acid, $\text{HOOC}(\text{CHOCH}_3)_2\text{COOH}$, so that in the trimethylglucose under consideration, two methoxyl groups must be situated on adjacent carbon atoms and only carbon atoms 2 and 3 are available for this purpose.

The number of methyl groups in these methylated compounds is determined by the ZEISEL method. By warming the methyl derivative with concentrated hydriodic acid, the methyl groups attached to oxygen are split off as methyl iodide; the latter is separated from the hydriodic acid present, and then treated with silver nitrate to produce silver iodide which is weighed.

Maltose is represented stereochemically by the following formula:

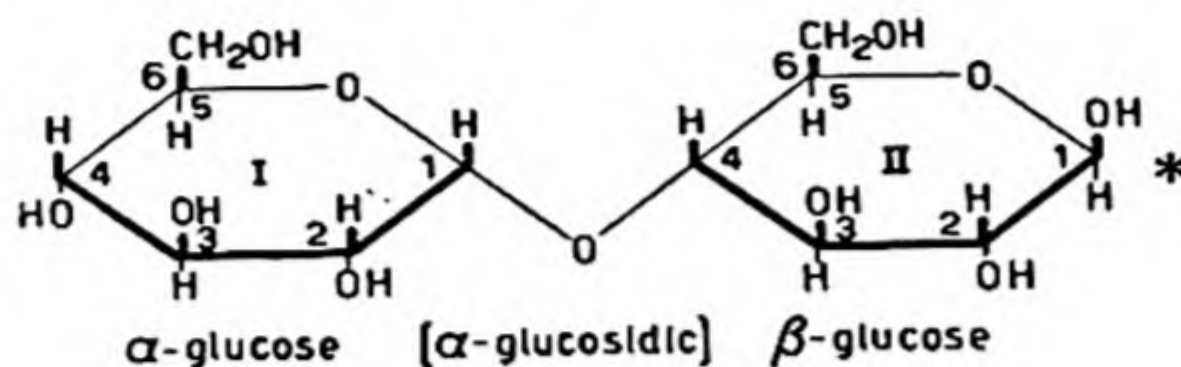


Fig. 49. Maltose

Since maltose is hydrolysed by the enzyme maltase but not by emulsinase and the former enzyme is specific for splitting α -glucosides while the latter splits β -glucosides (179), it is assumed that glucose residue I is combined in maltose as in an α -glucoside. Hence carbon atom I_1 has an α -configuration. Further, maltose has an increasing mutarotation like β -glucose. Hence carbon atom II_1 must have the β -configuration. Therefore maltose is an α -glucoside of β -glucose.

174. *Cellobiose* is a fission product of cellulose (see 186). The hexose residues in this molecule are also connected by oxygen bridges between carbon atoms I_1 and II_4 . This is demonstrated in exactly the same way as for maltose.

In cellobiose, glucose residue I is combined as a β -glucoside (see Fig. 50), since cellobiose is split up by emulsinase:

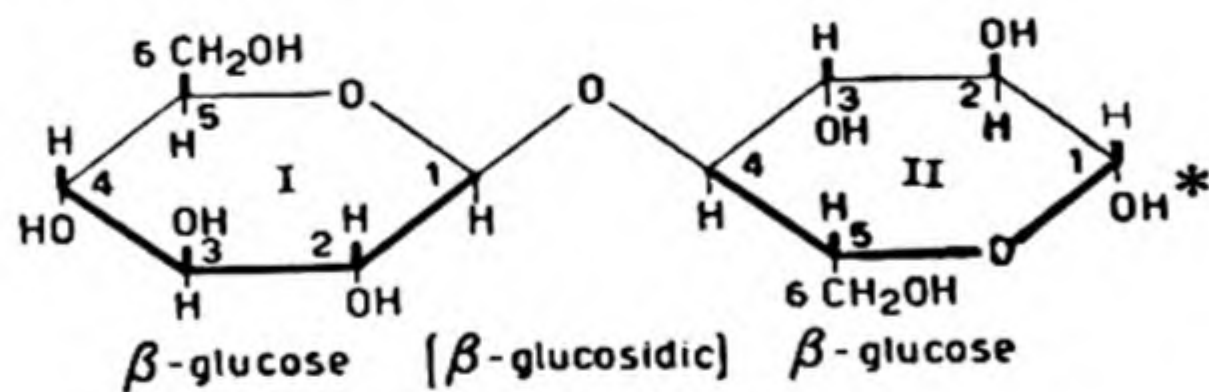
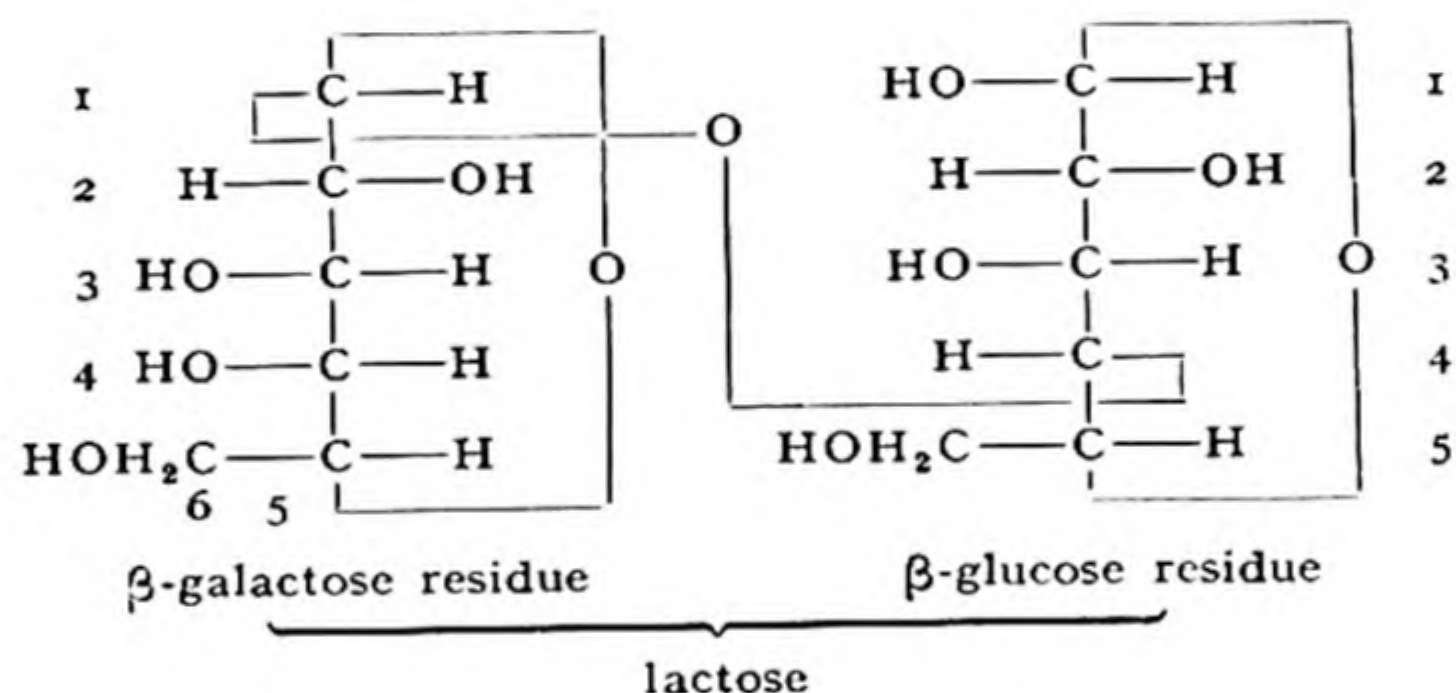


Fig. 50. Cellobiose

175. *Lactose* or *milk-sugar*. This disaccharide occurs to an extent of 4-5 % in milk and is prepared on a technical scale from it.

Whey is used for this purpose: this is the liquid which remains after the milk has been skimmed and after the *skimmed milk*, so obtained, has been used for making cheese. By these treatments the fats and the proteins in milk are to a large extent removed. The whey contains practically all the milk-sugar and a large proportion of the mineral constituents present in the milk. Milk-sugar is obtained by evaporating whey and is purified by recrystallising the product.

Milk-sugar crystallises with one molecule of water of crystallisation, in large, hard crystals. It is not so sweet as cane sugar and is split up on hydrolysis into *d*-glucose and *d*-galactose. It gives all the reactions of the monosaccharides and therefore contains a free reactive group in the molecule. This reactive group is present in glucose residue II, (Fig. 51), for on oxidation with bromine water, *lactobionic acid*, which is split up into *d*-galactose and *d*-gluconic acid on hydrolysis, is produced from milk-sugar. Since milk-sugar gives an osazone it follows that along with the reactive group on II₁, a free hydroxyl group must be present on carbon atom II₂. Galacto-arabinose, which easily forms an osazone, is produced by the oxidative degradation of lactobionic acid by FENTON'S method (162), so that a free hydroxyl group must be present on carbon atom II₃. Hence the galactose residue cannot be attached to carbon atoms 1, 2 or 3 of II, hence carbon atoms 4 or 6 remain to be considered. By methylating milk-sugar, an octamethyl-compound is produced, which gives 2,3,6-trimethylglucose on hydrolysis. Hence, from this it follows, that in lactose the galactose residue is joined to carbon atom 4 of the glucose residue:



Lactose shows mutarotation; both the α - and β -forms are known. The final value of the specific rotation is $+55.3^\circ$. Milk-sugar is split hydrolytically by *lactase*, an enzyme which is specific for splitting β -galactosides. It is therefore assumed that the galacto-residue in lactose is combined like a β -glucoside. The stereochemical representation of milk-sugar is given in Fig. 51.

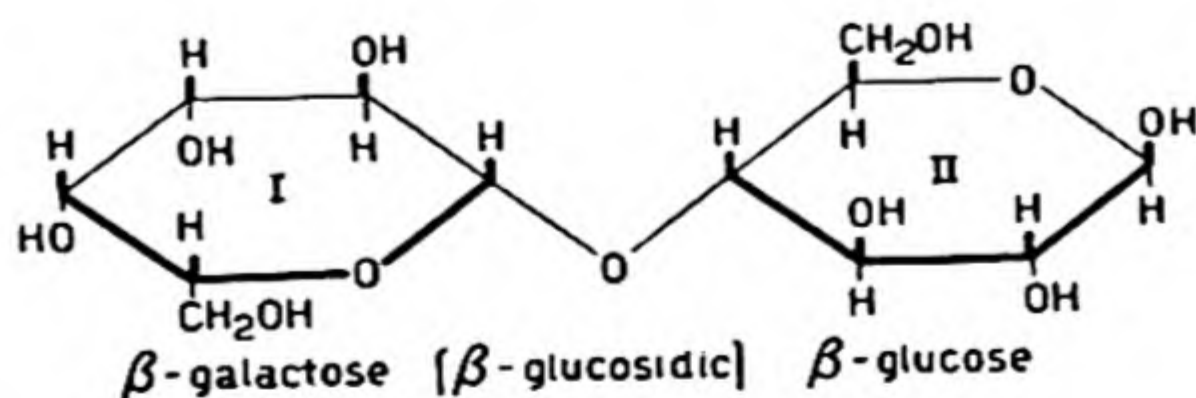


Fig. 51. Lactose

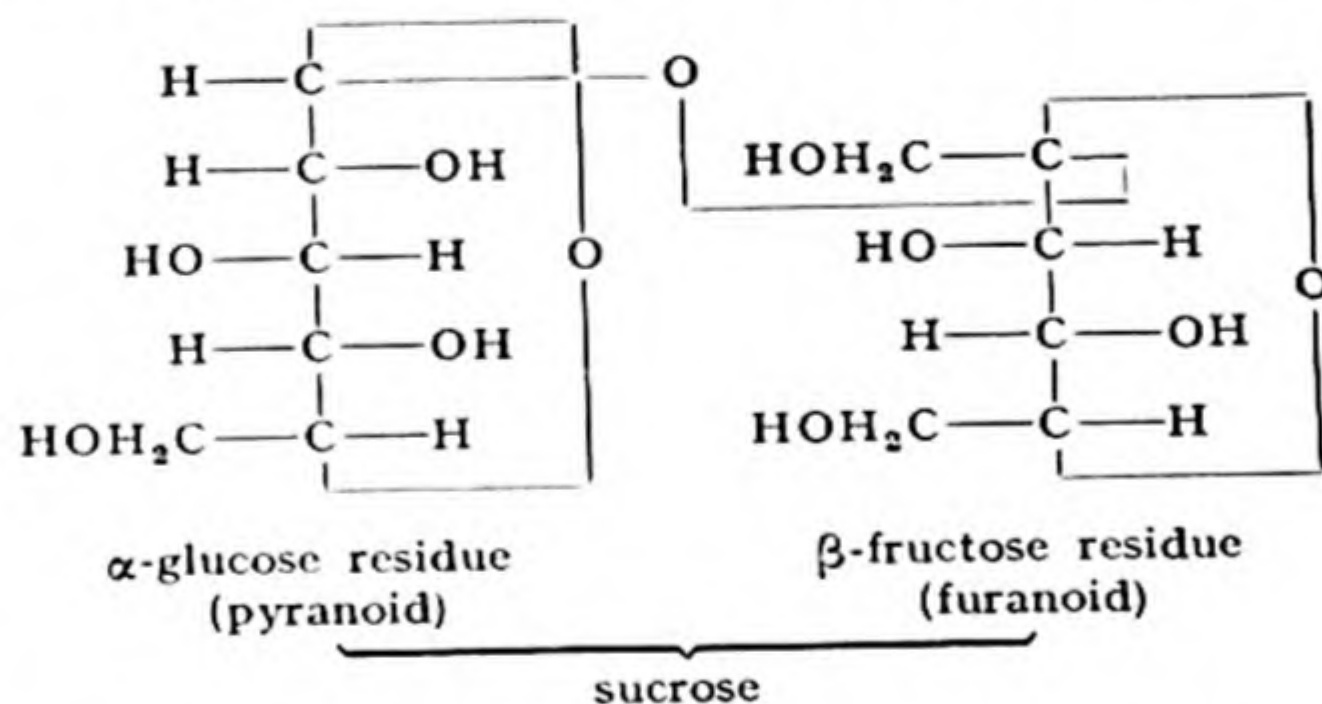
176. Sucrose or cane sugar. This sugar, which was obtained from the sugar-cane in India before the beginning of the christian era, occurs in very many plants and fruits. Sucrose can form large crystals (monoclinic), is very soluble in water, sparingly soluble in alcohol, and melts at 184° . When strongly heated, cane-sugar becomes brown in colour and is converted into a mixture of substances called *caramel*. By recrystallisation from methanol a metastable modification of cane-sugar, melting at 170° , can be obtained.

Compounds of cane-sugar with bases, called *saccharates*, are known, e.g. $C_{12}H_{22}O_{11}CaO_2H_2O$ and $C_{12}H_{22}O_{11}2CaO$, which are readily soluble in water. On boiling a solution of these soluble calcium saccharates, very sparingly soluble tricalcium saccharate, $C_{12}H_{22}O_{11}3CaO_3H_2O$, is precipitated.

Cane-sugar itself is strongly dextrorotatory, $[\alpha]_D = +66.5^{\circ}$; the mixture of equal parts of *d*-glucose and *d*-fructose (*invert-sugar*), which is produced from cane-sugar by hydrolysis, is laevorotatory because *d*-fructose rotates more to the left than *d*-glucose does to the right. As a result of hydrolysis the sign of the rotation is reversed; hence the name *inversion*. Invert-sugar is the chief constituent of honey.

Cane-sugar does not possess the characteristic reactions of the monosaccharides; it does not reduce an alkaline copper salt solution, it is not coloured brown by caustic alkalis and it does not give an osazone. Hence there are no reducing groups present in the molecule. From this it follows that both the reactive groups in the monosaccharide residues are involved in the mode of combination of the two residues.

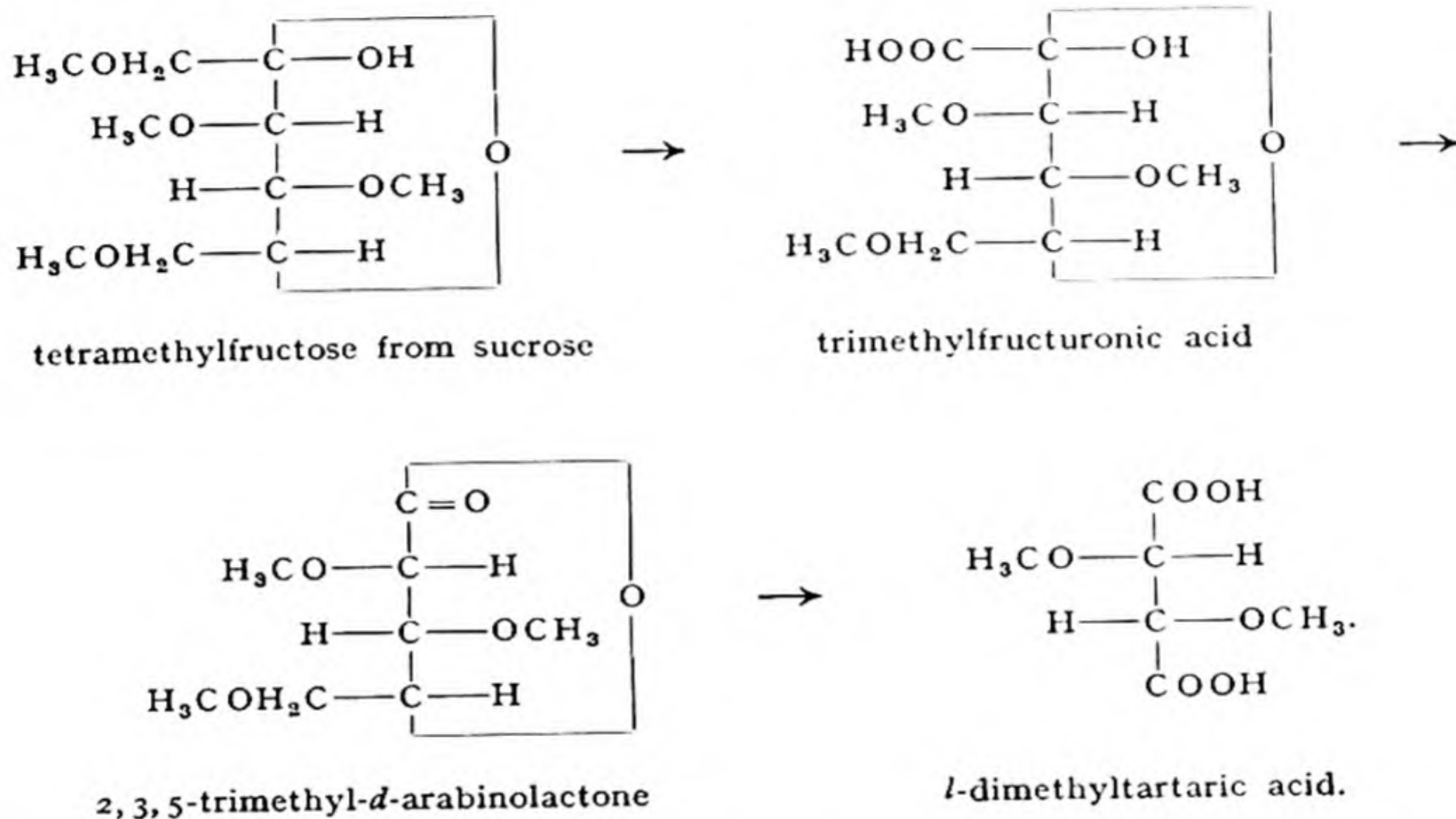
This is expressed in the following structural formula:



In this formula the epoxy-oxygen in the fructose residue is attached to carbon atoms 2 and 5. This was proved by HAWORTH as follows. By methylating sucrose, an octamethyl-derivative was produced from which tetramethylglucose and tetramethylfructose were obtained on hydrolysis. The tetramethylglucose appeared to be identical with the tetramethyl-compound produced by methylating glucose (**160**); from this it follows that the glucose residue in cane-sugar has the same structure as uncombined glucose. The

tetramethylfructose, a dextrorotatory liquid, was not identical with the tetramethyl-compound produced by methylating fructose; the latter is crystalline and laevorotatory.

On oxidising tetramethylfructose from cane-sugar with nitric acid, there is produced according to the reaction scheme given below, a *trimethylfructuronic acid*, which still possesses reducing properties. Further oxidation of this substance with permanganate in acid solution produces *2,3,5-trimethyl-d-arabinolactone*, which is converted into *l-dimethyltartaric acid* by oxidation with nitric acid:



We have here the remarkable fact that uncombined fructose has a different structure from the fructose combined in cane-sugar, which occurs in the furanoid form. When cane-sugar is hydrolysed by dilute acids the furanoid form of fructose passes over immediately into the pyranoid form. When the inversion is carried out by means of the enzyme *saccharase* (208), the rotatory power first of all rises rapidly and then slowly decreases until the usual final value is reached. The increase at the beginning indicates that a substance is first split off (furanoid fructose), which is dextrorotatory and eventually passes over into the stable laevorotatory (pyranoid) fructose:

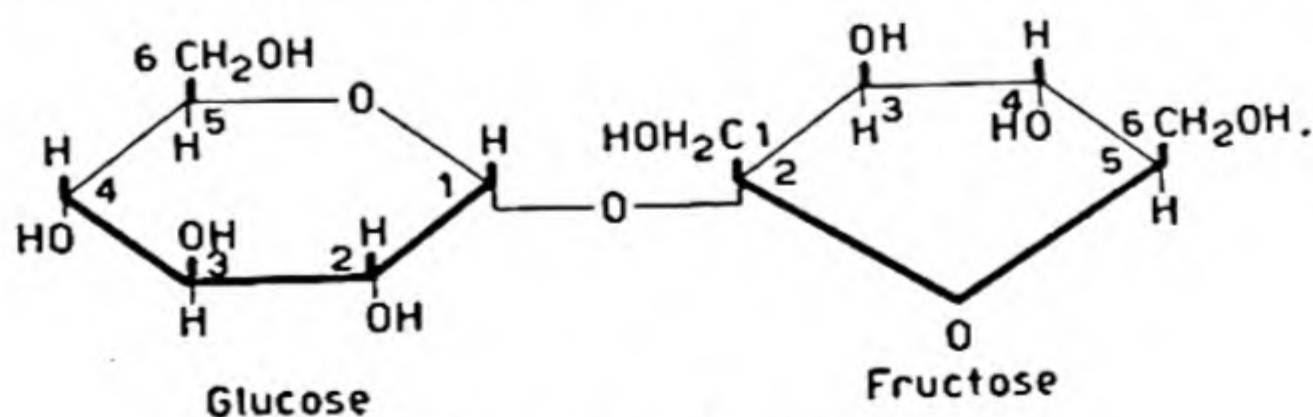


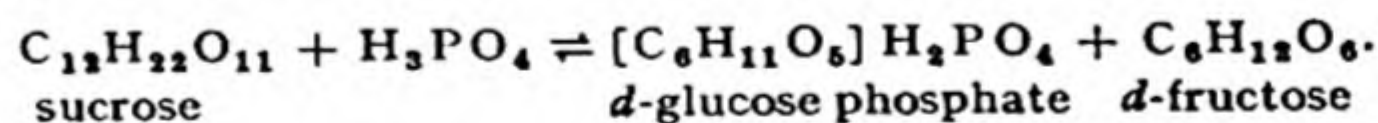
Fig. 52. Sucrose

On the basis of experiments on enzymatic fission, it is accepted that in sucrose, the pyranoid glucose residue is combined as an α -glucoside with a furanoid fructose residue occurring in the β -configuration.

Technical preparation of sucrose (beet-sugar or cane-sugar). Cane-sugar is prepared from the juice of the sugar-cane (e.g. in Java, Cuba, etc.). Beet-sugar is brought into solution in the diffusion process by extracting sugar-beet, cut up in small pieces, with water on the countercurrent principle. The juice is then purified, the aim being to remove the organic constituents which have passed into solution from the beet along with the sugar, since they hinder the crystallisation of the latter and the acids present would bring about inversion during the evaporation of the juice. To this end the juice is treated at an elevated temperature with an excess of milk of lime. By this means the acids are neutralised; besides the calcium salts of oxalic acid, citric acid and phosphoric acid, the proteins and colouring matters are to a large extent precipitated. The mixture is then treated with gaseous carbon dioxide to neutralise the excess lime. The purified juice, in order to prevent decomposition, is evaporated in *vacuum pans*. The juice of the sugar-cane is treated in the same manner. In this way *syrup* is produced, which is filtered and evaporated down further, again in vacuum pans, until crystallisation occurs. The sugar crystals, which are separated from the syrupy liquid, after cooling, by centrifuging, are practically colourless. The mother-liquors, syrups still containing a large amount of sugar, are evaporated down further to obtain a second crop of crystals. The final mother-liquor, (*molasses*), is worked up to alcohol. The crude sugar is dissolved in water and decolourised with decolourising carbon; the solution is then evaporated in vacuum pans when colourless crystals are obtained (refining). The *quantitative determination of cane-sugar* is carried out by means of a polarimeter (13). A 1 % solution shows a rotation of 0.665° in a 10 cm. tube. This rotation is proportional to the concentration, (which is not the case for very many other optically active substances) and varies very little with temperature.

177. Synthesis of disaccharides. The same enzyme which brings about the hydrolytic fission of a disaccharide into monosaccharides, can induce the formation of the disaccharide from the monosaccharides. BOURQUELOT obtained *gentiobiose* along with a little cellobiose by treating a concentrated solution of *D*-glucose with emulsinase. Gentiobiose, which occurs in gentian root, contains two glucose residues; the oxygen bridge is situated between carbon atoms I_1 and II_6 .

Biochemical synthesis of sucrose. From *Bacterium pseudomonas saccharophila* Doudoroff, a phosphorylase can be isolated, which is able to bring about the fission of sucrose by phosphoric acid:



This reaction takes a similar course to hydrolytic fission; instead of a molecule of water, a molecule of phosphoric acid takes part in the reaction. This is an example of *phosphorolysis*. *D*-Glucose-1-phosphate, in which the hydroxyl group on carbon atom 1 is esterified with phosphoric acid (CORI's

ester), is produced along with *d*-fructose. This phosphorolysis is reversible. In 1944 HASSID, DOUDOROFF and BARBER obtained *d*-sucrose by treating a mixture of *d*-glucose-1-phosphate and *d*-fructose with the above mentioned phosphorylase.

(c) *Trisaccharides and tetrasaccharides*

178. A few hexotrisaccharides of the formula $3C_6H_{12}O_6 - 2H_2O = C_{18}H_{32}O_{16}$, are known. Mention may be made of *raffinose*, which occurs in beet molasses, hence the name. Cotton-seed contains about 2.5 % of raffinose, which can be isolated by extraction with methanol. It is decomposed by hydrolysis with acids, with the participation of two molecules of water, into *d*-fructose, *d*-glucose and *d*-galactose. On careful hydrolysis with dilute acids or with saccharase, raffinose is converted into *d*-fructose and a disaccharide, *melibiose*.

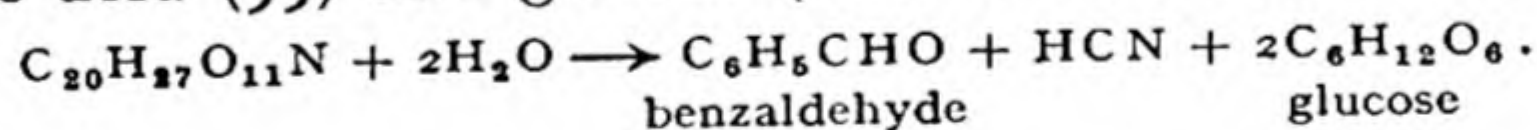
On hydrolysis, melibiose gives galactose and glucose: this disaccharide is α -galactosido-6-glucose. When raffinose is hydrolysed by emulsinase, cane-sugar and galactose are formed. Raffinose has no reducing properties; it crystallises with five molecules of water of crystallisation and has no sweet taste.

A tetrasaccharide, *stachyose*, $C_{24}H_{42}O_{21}$, occurs in the roots of *Stachys tubifera* and in manna.

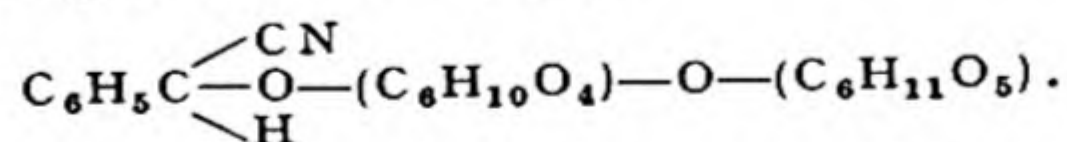
Glucosides

179. Certain compounds occur widely distributed throughout the vegetable kingdom, which are split up on hydrolysis into glucose (163) and a compound with an alcoholic hydroxyl group. These substances are called *glucosides*, a name which is frequently used even when the sugar produced on hydrolysis is a monosaccharide other than *d*-glucose. Glucosides also occur from which a disaccharide is produced on hydrolysis.

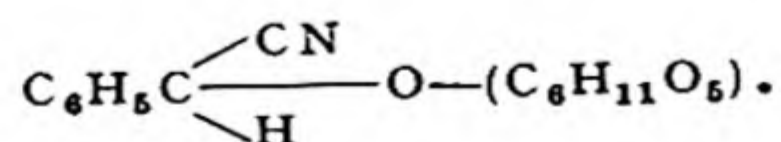
One of the earliest known glucosides is *amygdaloside*, $C_{20}H_{27}O_{11}N$, obtained from bitter almonds. In aqueous solution this substance is split up by *emulsinase*, an enzyme (208) also occurring in these nuts, into benzaldehyde (257), prussic acid (55) and glucose (LIEBIG and WÖHLER, 1837):



It has been found that amygdaloside is a glucoside of mandelonitrile (265) and the disaccharide gentiobiose (177):



When yeast extract is allowed to interact with amygdaloside, only one molecule of glucose is split off from the gentiobiose and *prunasin* (*prunaside*) (the glucoside of mandelonitrile), which also occurs in nature, is produced:



(d) *Polysaccharides*

180. Compounds belonging to this group occur widely distributed throughout the vegetable kingdom, *e.g.* *starch* and *inulin* as reserve-substances, *cellulose* as a constituent of the cell-wall, *lichenin* as a constituent of lichens and *pectin* (**188**) as a constituent of plant sap. *Glycogen* (**184**), a substance closely related to starch, occurs in the animal organism.

These substances are amorphous in appearance, although X-ray examination has shown that most of them possess a crystalline structure.

Cellulose is quite insoluble in water, starch passes into colloidal solution in warm water, inulin and glycogen are also soluble in water giving colloidal solutions, while among the pectins there are substances which are soluble in water and others which are insoluble. The physical properties of these substances therefore are quite different from those of the sugars and incidentally they do not possess a sweet taste. These compounds are polysaccharides because they are broken down to monosaccharides by hydrolysis.

The composition of these polysaccharides is represented by the formula $(C_6H_{10}O_5)_n$ in which n expresses the fact that the molecular weights are high.

181. *Starch* $(C_6H_{10}O_5)_n$. Starch is formed in the assimilation process in plants from carbon dioxide and water; it is present in large quantities in roots, tubers and seeds of very many species (potatoes, grain, tapioca, rice, sago, etc.). Starch occurs in the plant in granules differing in size (0.5–170 μ) and appearance depending on the species of the plant, as shown in Figures 53 and 54.

In its original state, starch is very sparingly soluble in cold water but in warm water, the starch-granules swell considerably to form a gel (starch paste); on warming further and in presence of sufficient water, a colloidal solution (sol) is formed which sets to a gel on cooling. This swelling of the starch grain and the formation of a gel is the basis of *starching* fabrics.

Thus starch is not molecularly dispersed in solution. It is accepted that during the process of solution, water penetrates in between the starch particles, which consist of aggregates of molecules and which are called *micelles*, a term suggested by NÄGELI; the size of the particles or micelles in starch sols is affected by various factors and is not the same for different kinds of starch.

On warming with water, the starch granules undergo a change which can be followed microscopically; on swelling the starch granule appears to grow into a sac with an elastic wall enclosing a colloidal solution (A. MEYER, BEYERINCK). By warming starch with water more strongly, or under the influence of certain swelling agents, eventually the wall of the sac breaks down and is dispersed also. From the formation of vesicles in the solubilising process, it is concluded that starch consists of two constituents, *amylopectin*,

forming the membrane of the vesicle and *amylose*, which collects as a colloidal solution inside the membrane (MAQUENNE). This view, however, is no longer

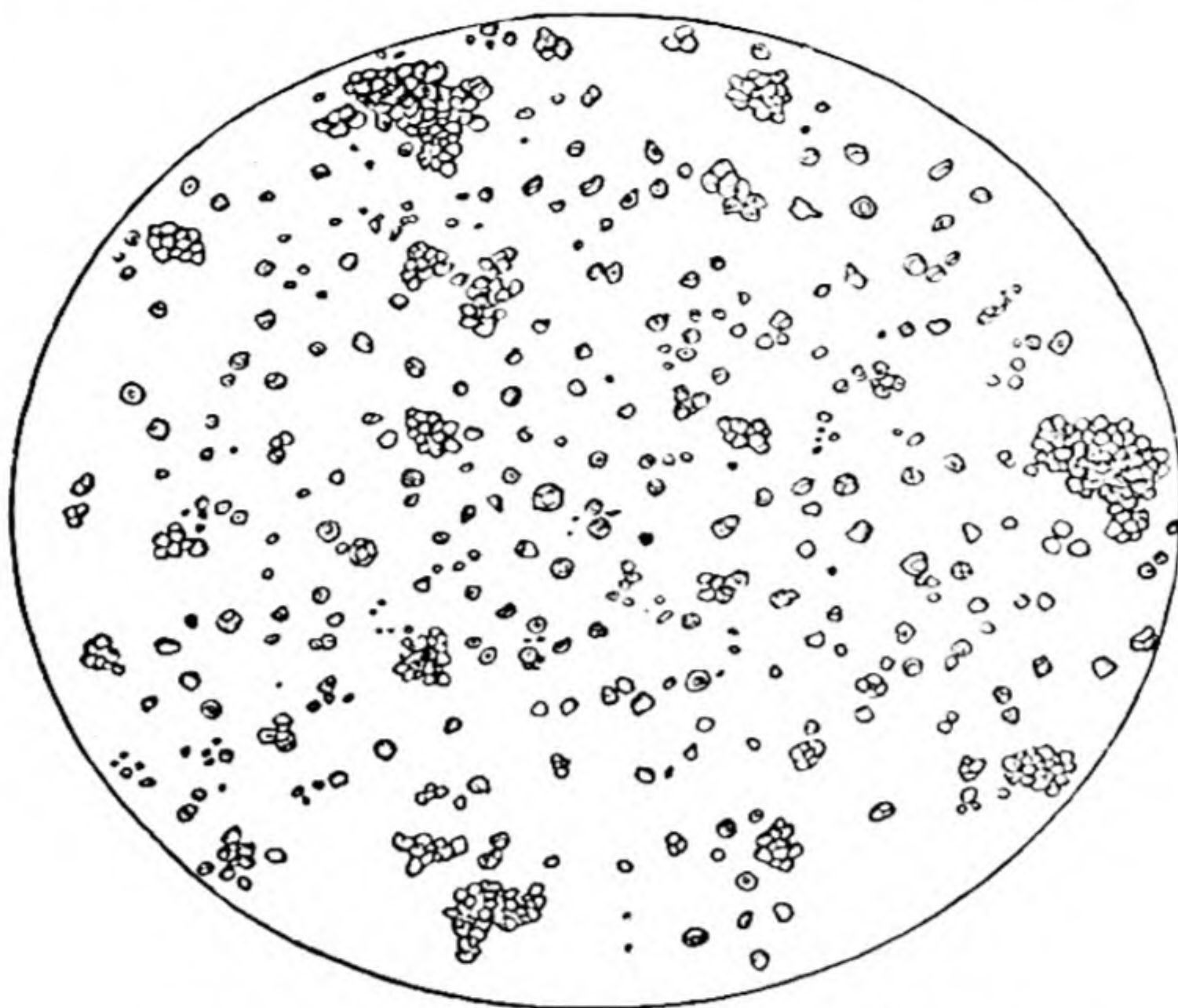


Fig. 53. Rice starch ($\times 320$, linear)

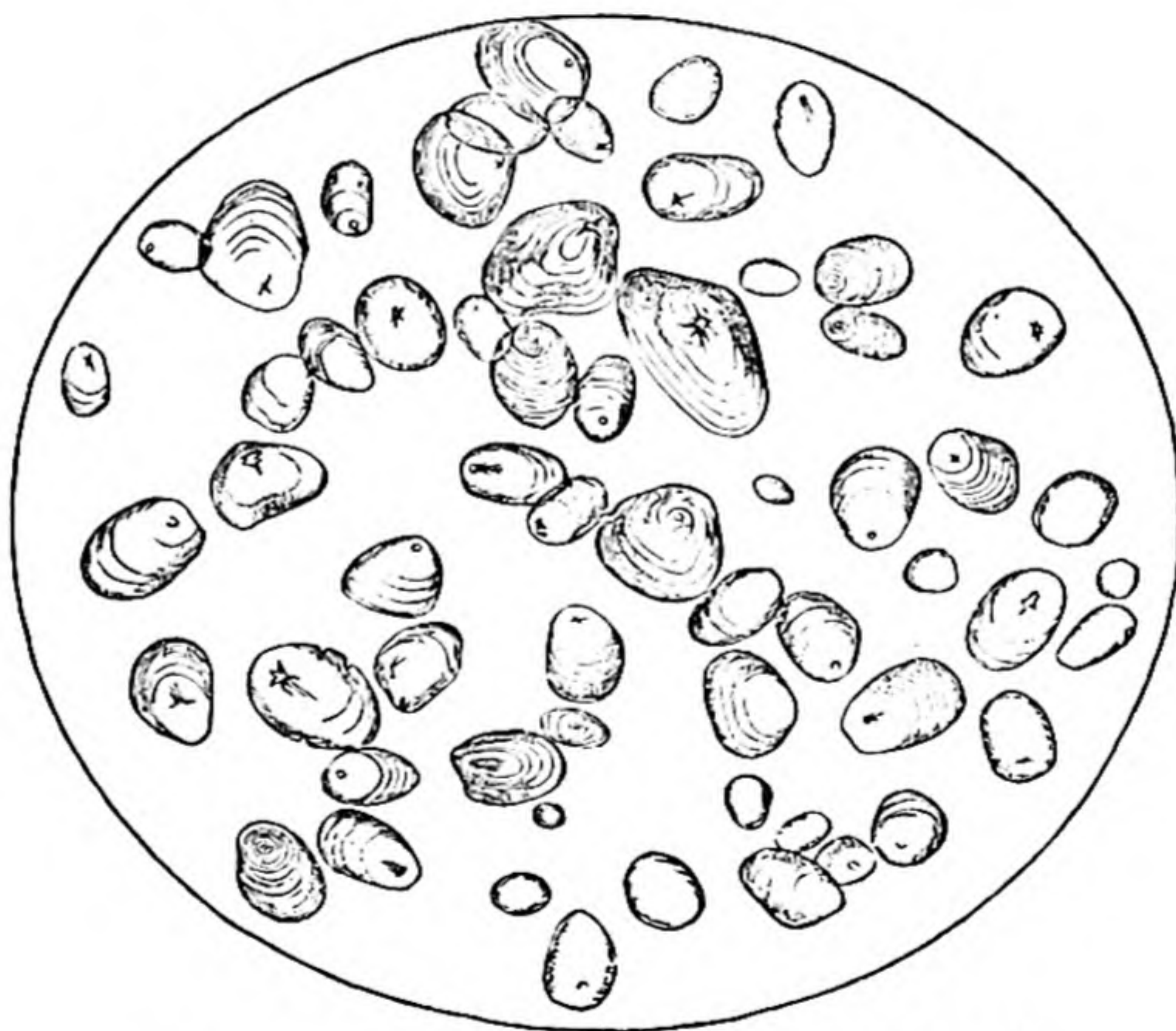


Fig. 54. Potato starch ($\times 250$, linear)

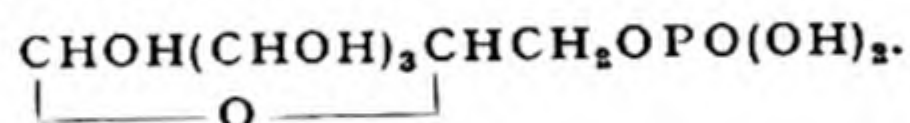
tenable: from microscopic examination it appears that the unswollen starch granule does not possess a skin with special properties (BADENHUIZEN).

Since the various layers in the starch granules have identical properties, amylopectin must be distributed in a regular manner throughout the whole granule. Both have the composition $(C_6H_{10}O_5)_n$.

The two constituents may be separated from each other almost completely by electrodialysis (SAMEC), or still better by treatment with *n*-butanol (SCHÖCH), thymol (HAWORTH), or a number of other substances. A precipitate is then formed, since the amylose adsorbs the added substance and so becomes insoluble, while the amylopectin remains in solution. In general, the amylose content of starch is 20–30 %. The starch from the so called "adhesive varieties" of a number of cereal crops (rice, maize, barley, etc.) consists entirely of amylopectin, while that from crinkled varieties of peas consists almost exclusively of amylose.

The composition of starch is not expressed exactly by the empirical formula $C_6H_{10}O_5$, since all varieties of starch contain a very small amount of combined phosphorus. For potato starch the phosphorus content is 0.06–0.09 %. This phosphorus is present in the form of phosphoric acid with one of its hydroxyl groups esterified with a $—CH_2OH$ group in one or more glucose residues in the starch molecule.

From the reaction product resulting from the hydrolysis of potato starch with amylase, POSTERNAK was able to isolate the phosphoric esters of a hexasaccharide and of a tetrasaccharide, viz. $C_{36}H_{61}O_{30}[OPO(OH)_2]$ and $C_{24}H_{41}O_{20}[OPO(OH)_2]$. The latter could be split up further by hydrolysis with dilute sulphuric acid, whereby a phosphate ester of glucose was produced:



This compound appears to be identical with a phosphate ester of glucose observed as an intermediate product in alcoholic fermentation (HARDEN, ROBISON). Its structure has been established by synthesis.

Wheat starch contains about as much combined phosphorus as potato starch. On hydrolysing wheat starch, however, the above mentioned phosphate esters of polysaccharides are not found but a phosphate ester of glycerol is isolated. Wheat starch also contains small quantities of phosphatides (119), which are probably combined with the carbohydrate constituent of the starch molecule.

The blue colouration produced on starch by a solution of iodine in potassium iodide solution is caused mainly by amylose: amylopectin and the starches from the adhesive varieties are coloured reddish violet and take up iodine with much greater difficulty than amylose. The reaction probably depends on adsorption phenomena since a similar blue colouration is observed with iodine and a number of colloidal substances of very varied chemical character. It should also be mentioned that the blue colour produced with iodine and starch disappears on warming to 70° and reappears again on cooling.

182. Structure of starch. A colloidal solution of starch is optically active and dextrorotatory. The reducing power is extremely small but unmistakable, so that very few reducing groups are present. When starch is boiled with dilute acids it is split up giving a practically quantitative yield of *d*-glucose, showing that both constituents of the starch give this hexose on hydrolysis.

This fission was discovered by KIRCHHOFF in 1811. In the fission of starch by malt extract—in which *diastase* occurs (31, 173, 184, 208)—maltose is the main product; *isomaltose*, in which the two glucose residues are joined by a 1,6- α -glucosidic bond, is the only other disaccharide, which has been detected with certainty (MYRBÄCK).

Intermediate products, the *dextrins*, are produced by hydrolysis either by acids or by diastase. These dextrins are colloidal substances, the size of the particles being smaller than in the original starch but varying over wide limits. The products isolated as dextrins are in all probability not pure chemical substances but mixtures. When their molecular weight is above a certain limit, the dextrins are precipitated from aqueous solution by alcohol in the form of amorphous flocks; they are coloured reddish brown by iodine.

By the action of a mixture of acetic anhydride and acetic acid on amylose or amylopectin, a triacetate of the composition $[C_6H_7O_2(OOCCH_3)_3]_n$ is produced; if this triacetate is treated with alkali and dimethyl sulphate the acetyl residues are replaced by methyl groups giving a trimethyl-derivative of starch $[C_6H_7O_2(OCH_3)_3]_n$. From these experiments it may be concluded that starch contains three hydroxyl groups per $C_6H_{10}O_5$ group. 2,3,6-Trimethylglucose along with a small quantity of 2,3,4,6-tetramethylglucose is produced on hydrolysing trimethylstarch with dilute acids (HAWORTH). From this it follows that the glucose residues in starch have the pyranoid structure (like 2,3,6-trimethylglucose) and that the successive glucose residues in the starch molecule are joined together by oxygen atoms between carbon atoms 1 and 4.

Therefore the starch molecule contains one or more chains of glucose residues joined together as α -glucosides (HIRST, HAWORTH).

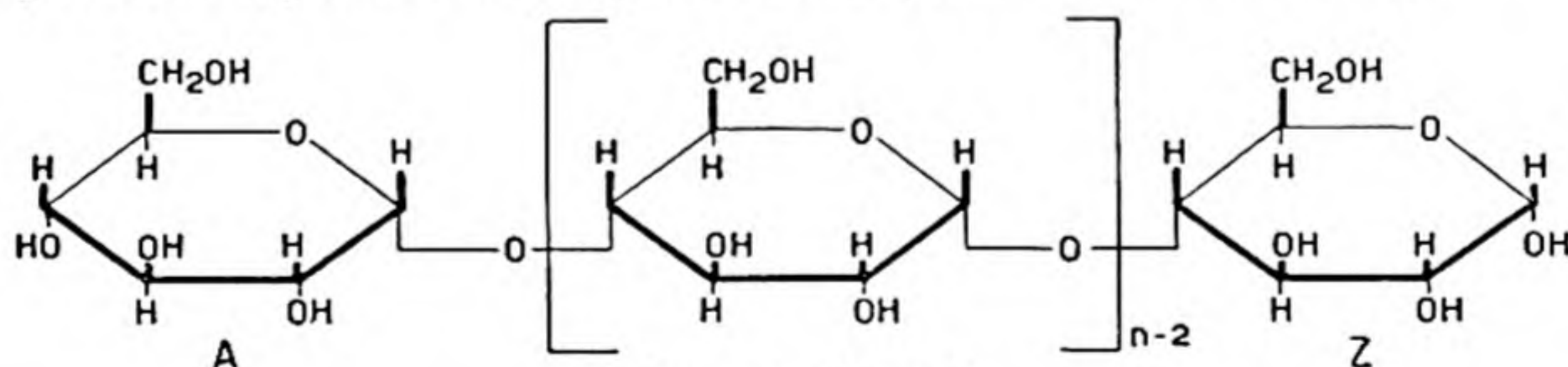


Fig. 55. Starch

The tetramethylglucose, found on hydrolysis of trimethylstarch, is derived from the glucose residue A, which contains four free hydroxyl groups. Practically the same quantity of tetramethylglucose is found with different preparations of trimethylstarch, obtained by methylation of various kinds of natural starch, notwithstanding that the preparations examined showed great differences as regards the viscosity of their solutions and the size of the dissolved particles. From the amount of tetramethylglucose obtained, it

follows that the chain from which it is split contains 24–30 glucose residues. Osmotic measurements, however, show that starch molecules have a much higher molecular weight than corresponds with the above result.

Also the very small reducing power, due to the glucose residue Z (Fig. 55), indicates a molecule containing many more than 30 glucose residues. This contradiction is resolved by assuming a branched chain structure for the starch molecule, in which the branches contain on the average 27 glucose residues (STAUDINGER). In agreement with this suggestion, it has been found that very small quantities of 2,3-dimethylglucose are also found in the hydrolysis products of trimethylstarch, which makes it probable that the terminal group of the side chain Z is attached by its first carbon atom to carbon atom 6 of a non-terminal glucose residue. These branching places provide the isomaltose (p. 287) produced in the hydrolysis of starch.

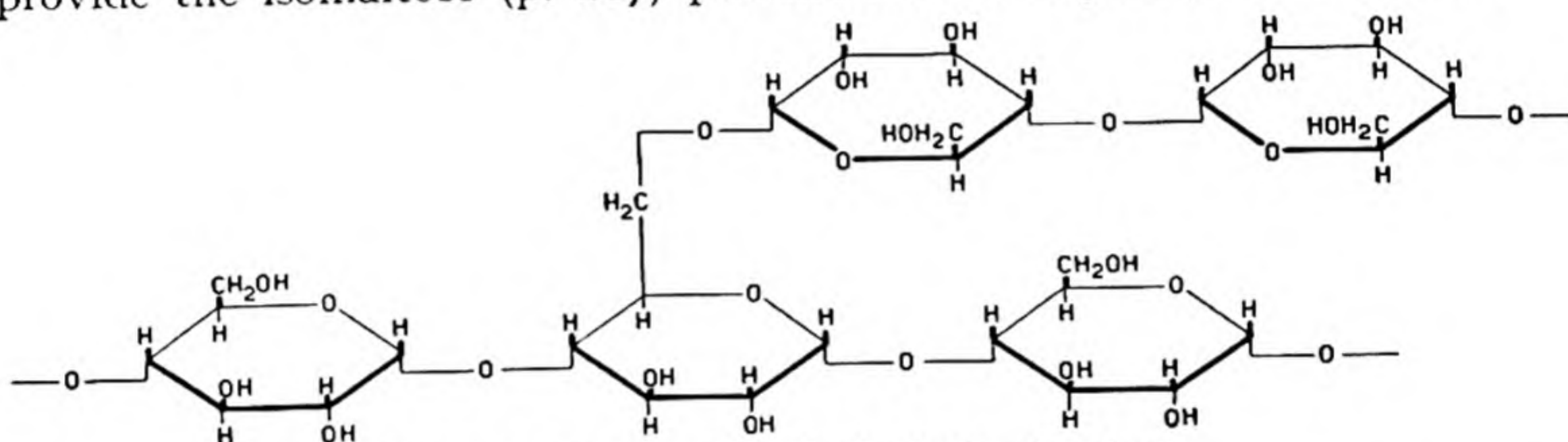
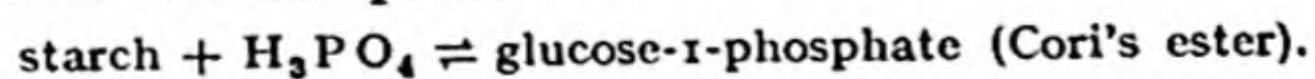


Fig. 56. Starch, branched chain structure

After satisfactory methods had been found for separating the two components, amylose and amylopectin, it was possible to study these compounds separately. From osmotic measurements it follows that *amylose* has a molecular weight not exceeding 50,000 corresponding with a chain length of about 250 glucose residues. After methylation and hydrolysis, 0.4 % of tetramethylglucose is found, so that 0.4 % of the total amount of glucose occurs as a non-reducing terminal group, *i.e.* in the ratio of 1 : 250. From this it follows that amylose consists of unbranched chains. This is confirmed by measuring the reducing power, when it is found that there is only one reducing group per 250 glucose units.

The molecular weight of *amylopectin* on the other hand, is round about 300,000; the molecule contains 3.8 % of tetrahydroxy-terminal groups and only one aldehyde grouping to 1500 to 3,000 glucose residues. On the average this corresponds with an aldehyde group to about 100 tetrahydroxy-terminal groups. These facts can only be explained if it is assumed that the amylopectin molecule is branched. Hence starch consists of unbranched chains (amylose) and branched chains (amylopectin) (Fig. 56).

Besides being broken down by amylase with the addition of water (hydrolysis), starch can also be decomposed by *phosphorylases*, occurring in plants and in animals with the addition of phosphoric acid (*phosphorolysis*). Unlike enzymatic hydrolysis, phosphorolysis is a reversible process:



In this way starch has been prepared *in vitro* (HANES). The synthetic reaction can only occur if polysaccharides corresponding in structure are added previously to act

as "seeds". At first only unbranched chains were obtained, but after the discovery of a phosphorylase which would produce amylopectin, this component also was prepared (PEAT and BOURNE).

183. *Technical preparation of starch from potatoes.* The latter are finely grated to rupture the cell tissues and allow the starch granules to escape. By treatment with cold water the starch granules are washed out of the tissue in sieves. The water containing the starch is allowed to flow into large vats in which the starch settles and is washed and eventually dried.

Starch is used as a foodstuff, for the preparation of prepared starch and in industry for finishing cheap fabrics and paper. It is also worked up into dextrin, which is used as an adhesive, and into glucose syrup (plain syrup, potato syrup).

Starch is an important constituent of many foodstuffs. Wheaten flour consists chiefly of this material (about 80 %) and protein (gluten). During the baking of bread the starch extracts the water from the dough and in so doing the granules swell up and jellyfy. The proteins from the gluten solidify so that in the bread a continuous network of protein is produced which is held together by the swollen starch granules.

184. *Glycogen* $(C_6H_{10}O_5)_n$ is a polysaccharide which occurs in the animal organism, chiefly in the liver (CLAUDE BERNARD, 1857). Lower plants, especially moulds, also contain glycogen. The latter can be isolated from liver by boiling with concentrated potash, which destroys the liver tissue but leaves the glycogen unattacked. In its chemical behaviour, glycogen is very similar to starch. It dissolves in cold water to form a colloidal solution but it does not form a starchlike gel such as is observed with starch. Glycogen contains no phosphoric acid. The colloidal solution of glycogen does not reduce FEHLING's solution appreciably, it is optically active and dextrorotatory.

d-Glucose is the sole product obtained by hydrolysing glycogen with dilute acids and maltose is the main amylolytic degradation product. In a similar way to that used for amylopectin, it has been possible to show that the glucose residues are combined by α -glucosidic bonds in branched molecules. The glycogen molecules differ from those of amylopectin only slightly in that the degree of branching is higher in the case of glycogen and the branches are shorter. Otherwise the configurations agree. A phosphorylase is met with in livers and hearts, which is able to bring about the production of glycogen *in vitro* (CORI).

185. *Inulin* $(C_6H_{10}O_5)_n$. This carbohydrate occurs in dahlia tubers, from which it can be prepared and it is also met with in many other plants (*e.g.* in *helianthus tuberosus* and in artichokes). It dissolves to a colloidal solution in water, the solution is laevorotatory and shows no reducing power. *d*-Fructose is formed exclusively by hydrolysis with dilute acids; by hydrolysing trimethylinulin the same furanoid trimethylfructose is produced as is obtained from octamethylsucrose(176). Hence the fructose residues in inulin have the furanoid structure.

186. *Cellulose* $(C_6H_{10}O_5)_n$. The cell walls of plants consist chiefly of *cellulose* and *lignin*. Linen and cotton consist for the greater part of cellulose. Filter paper, which consists of practically pure cellulose, is attacked by concentrated sulphuric acid and converted into a soluble product. If this solution in sulphuric acid is diluted with water and boiled, hydrolysis takes place

and *d*-glucose is produced as the final product. The formation of a sugar-like substance by the action of sulphuric acid on linen was observed by BRACONNOT in 1819.

When the hydrolysis of cellulose is carried out by means of 41 % hydrochloric acid at low temperatures, the theoretical quantity of glucose is produced; when this hydrolysis is carried out very carefully a trisaccharide $C_{18}H_{32}O_{16}$ and a tetrasaccharide $C_{24}H_{42}O_{21}$ can be produced (WILLSTÄTTER; ZECHMEISTER).

Cellulose is very slowly hydrolysed by an enzyme *lichenase*, which is present in the alimentary canal of the vine-slug (*Helix Pomatia*). In this enzymatic fission which takes place more rapidly with cellulose precipitated from cuprammonium solution, a practically quantitative yield of *d*-glucose is produced.

From the actual cellulose it is possible to distinguish the so-called *hemicelluloses*, also insoluble polysaccharides, which occur as constituents of the cell walls of plants; these hemicelluloses are hydrolysed by warm dilute acids with the formation of *d*-glucose and other monosaccharides such as *d*-galactose and *d*-mannose.

No solvents are known which will dissolve cellulose without its undergoing some modification. Cellulose is soluble, however, in an ammoniacal solution of copper oxide (SCHWEITZER's reagent); the solution so obtained, contains a complex copper ammonium compound of cellulose comparable with the copper alkali compounds from glycerol and the saccharides. Cellulose is reprecipitated from this solution by acids; the cellulose so obtained has the same composition as the original cellulose but in some respects it possesses different properties.

On treatment with approximately 70 % sulphuric acid for a short time followed by washing with water, cellulose is converted into a colloidal decomposition product, which is coloured blue by iodine and is therefore called *amyloid*. This property can be made use of for testing for cellulose.

187. Structure of cellulose. Cellulose contains free hydroxyl groups; this is shown by the formation of esters with both organic and inorganic acids. When cellulose, *e.g.* cotton wool, is heated with acetic anhydride and a little zinc chloride, a cellulose acetate is produced corresponding with the composition $[C_6H_7O_2(COOCH_3)_3]_n$. Under other conditions, acetylation produces a mixture of various cellulose acetates but no more than three acetyl groups can be introduced into each $C_6H_{10}O_5$ unit.

When cotton is treated with a mixture of concentrated sulphuric acid and nitric acid, a mixture of cellulose di- and tri-nitrates, the so called *nitro-celluloses*, in varying proportions depending on the concentration and the duration of the reaction, is produced. The final product in this reaction is *cellulose trinitrate* the composition of which corresponds with $[C_6H_7O_2(ONO_2)_3]_n$. It is noteworthy, that in this reaction the original fibrous structure of the

cellulose persists in the reaction product; cellulose trinitrate prepared from cotton wool has the same appearance as the starting material; the fibrous structure is maintained also in cellulose acetates.

In the methylation of cellulose it has been possible to obtain a trimethyl-cellulose, the methoxyl content of which practically agrees with the formula $[C_6H_7O_2(OCH_3)_3]_n$ (DENHAM, IRVINE, FREUDENBERG, HAWORTH). From all these observations therefore, it follows that cellulose has such a structure that three free hydroxyl groups are present in each $C_6H_{10}O_5$ unit.

A study of the acetylative degradation of cellulose led to an important result (FRANCHIMONT; SKRAUP). When the acetylation is carried out with acetic anhydride and concentrated sulphuric acid, the octa-acetyl-compound of cellobiose (see 174) is produced from which cellobiose itself can be prepared by hydrolysis with alcoholic potash. Besides cellobiose acetate, acetolysis also produces a small quantity of the acetate of a trisaccharide (BERTRAND).

By hydrolysing trimethylcellulose with dilute hydrochloric acid at 0° , a mixture of methylated glucoses is produced, which may be converted into methylated methylglucosides (160). This mixture of methylated glucosides is separated into its components by distillation in a high vacuum. In this way HAWORTH obtained 2,3,6-trimethylglucose along with a small amount of tetramethylglucose. By another method of decomposition he obtained from trimethylcellulose, a *decamethyl-methylcellotrioid*, which was split hydrolytically into one molecule of tetramethylglucose and 2 mols. of trimethylglucose.

All these facts are in agreement with a formula for cellulose put forward by HAWORTH and also by MEYER and MARK, in which glucose units are combined like β -glucosides as in cellobiose (see Fig. 57):

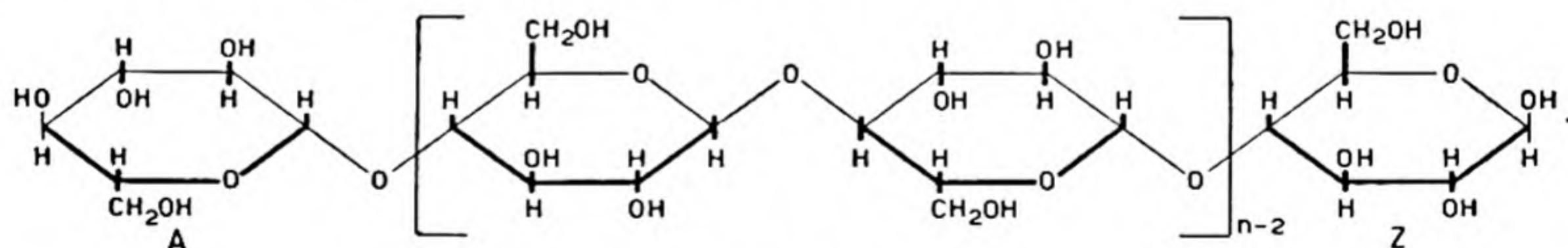


Fig. 57. Cellulose

If the molecule of cellulose consists of an open chain of n glucose units, the composition is represented by $n(C_6H_{12}O_6) - (n-1)H_2O$, and for large values of n this composition approximates to that of $C_6H_{10}O_5$, the empirical formula for cellulose derived from elementary analysis.

From the formula given above, it follows that all the glucose residues have three free hydroxyl groups except the terminal one in which four free hydroxyl groups must be present. Hence, strictly speaking, on complete methylation a methylcellulose should be obtained having a methoxyl con-

tent rather greater than is calculated for a substance of the formula $C_6H_5O_2(OCH_3)_3$, the accuracy of the experiments, however, is not nearly high enough to detect such a small difference. The small amount of tetramethylglucose produced by the hydrolysis of trimethylcellulose is derived from glucose residue A.

The number of glucose units involved in building up the chain-like molecules occurring in natural cellulose fibres, is not known; this number is assumed to be about 3,000. In cellulose preparations such as *rayon*, which is prepared from natural cellulose, the length of the chain-like molecules is much smaller.

In the above formula, the terminal group in the chain (Z) contains a reducing group. Natural cellulose shows no reducing properties; the nature of the terminal group is not known. The presence of reducing terminal groups can be shown in preparations produced by partial hydrolysis.

The nitrates, acetates and the methyl ethers of cellulose form colloidal solutions in certain organic solvents. The dissolved substance does not consist of one molecular species but of molecules of different sizes varying in chain length (polymer homologues). Methods of measuring the small osmotic pressures of these colloidal solutions have been worked out by various investigators, *e.g.* by E. H. BUCHNER. The values calculated from these results for "the average molecular weight" of various cellulose derivatives diverge very considerably depending on the specimen used and the solvent. Values from 40,000 to 110,000 have been found for cellulose triacetate and from 54,000 to 110,000 for cellulose nitrates, and it is undecided whether the colloiddally dissolved substance is present as molecules or as aggregates of molecules.

Important conclusions have been reached from investigations on the X-ray spectra of cellulose fibres (SCHERRER, POLANYI, K. H. MEYER, H. MARK, SPONSLER, P. H. HERMANS). A cellulose fibre is built up of very small crystals (micelles or crystallites) with the same crystallographic axis lying almost parallel with the axis of the fibre, while the remaining axes take up different positions in a direction perpendicular to it. These crystallites consist of bundles of cellulose molecules of different chain lengths; these chain-like molecules are arranged with their long axis roughly parallel to the axis of the fibre. The length of the elementary cell in the crystallites is 10.3 Å, which corresponds with the length of a cellobiose chain.

The crystallites in cellulose nitrate and cellulose acetates are also arranged parallel with the fibre axis (J. R. KATZ).

188. *Lichenin* or *reserve cellulose* occurs in many species of moss and also in smaller quantities in higher plants.

On hydrolysis it is completely decomposed into glucose, while partial hydrolysis with acetic anhydride and sulphuric acid converts it, like cellulose, into cellobiose. Lichenin is much more readily attacked by enzymes (the so-called lichenases) than is cellulose. Lichenases occur fairly wide spread in the vegetable kingdom and also in the animal kingdom in invertebrates. Reserve cellulose is converted into sugars by lichenase.

Pectins. Under this name is grouped a number of vegetable substances of high molecular weight, which are closely related to the polysaccharides.

In the soluble form, pectins occur in fruit juices; they easily form gels and are used therefore in making fruit jellies. Insoluble pectins occur in the form of calcium or magnesium salts in the green parts of plants and in roots. On hydrolysing pectins, methanol, *l*-arabinose, *d*-galactose and *d*-galacturonic acid, *i.e.* an aldehydic acid derived from *d*-galactose, are produced. *Galactan* and *araban* (*i.e.* polysaccharides derived respectively from galactose and arabinose 163), occur in pectins mixed with or adsorbed on *pectic acid*. The latter is a compound of high molecular weight, in which galacturonic acid residues are joined together through oxygen atoms to form a chain and in which —COOCH_3 groups occur as well as carboxyl groups.

189. *Lignin.* Wood consists mainly of cellulose, which may account for about two thirds of the dry material; it also contains 1-2 % of *xylan* (163) and *lignin* (up to 30 %).

When wood is treated with very concentrated hydrochloric acid, the cellulose is hydrolysed and the lignin remains behind as a dark brown amorphous mass. Lignin obtained in this way is not a chemical individual but a mixture of probably closely related substances.

The structural formula for lignin is not yet known. Lignin has a higher carbon content than the carbohydrates and the molecule is partly constructed of substituted benzene nuclei; this is apparent from the fact that 3,4-*dihydroxybenzoic acid* (263) is produced along with oxalic acid when the substance is fused with potash. Lignin contains in addition, methoxyl groups (15-20 %) and hydroxyl groups. The methanol produced in the dry distillation of wood is a decomposition product of lignin.

Characteristic reactions for lignin are the production of a yellow colour with aniline and of a red colour with a solution of phloroglucinol in concentrated hydrochloric acid.

Technical applications of cellulose. Cellulose nitrates; artificial silk.

190. *Linen* is obtained from the stalks of the flax plant. On account of the stability of cellulose the linen fibre can be separated from flax by rotting (technically termed *retting*). The separated fibre, which is greyish in colour, is bleached either by exposure to sun and air or by treatment with bleach liquor.

At one time *paper* was made almost exclusively from linen rags, but at the present time a great deal is made from wood-pulp or straw. For this purpose the cellulose must be isolated from the wood and separated as well as possible from substances, which occur alongside it in the wood (*encrusted substances*) and which consist mainly of lignin. This is accomplished by the sulphite method, in which wood is heated under pressure with a solution of calcium bisulphite. When straw is used as the basis for paper, it is heated under pressure with sodium hydroxide solution. By these means the encrusted substances are to a large extent decomposed and the greater part of

the decomposition products pass into solution, at the same time the wood or straw is bleached and the cellulose remaining behind is easily divided into fine fibres such as are required for making paper pulp. It is not possible, however, to remove the lignin completely in this way, hence paper made of these starting materials still shows the characteristic reactions of lignin and can be easily recognised as a consequence (189).

Parchment paper is paper in which the surface has been converted into amyloid in the way given in 186 to give it rigidity. After treatment with concentrated sulphuric acid it must of course be thoroughly washed immediately.

When cellulose (cotton fibres) is treated with concentrated sodium hydroxide solution and then washed with water, it is altered in properties although it remains the same in composition. This *mercerised* cellulose (so-called after the discoverer of this reaction, MERCER) can take up water like swellable material and it takes up dyestuffs more readily than ordinary cellulose. For these reasons the mercerisation of cotton is of great importance for cotton dyeing.

The *nitrates of cellulose*, which are usually designated by the incorrect name of *nitrocelluloses*, are of great technical importance. By the action of a mixture of nitric and sulphuric acids on cotton, a mixture of mono-, di- and tri-nitrates of cellulose is produced, the composition depending on the concentration of the acid employed and the duration of the treatment.

A product with a nitrogen content of 8–10 % consisting mainly of the di-nitrate, is *collodion*. This substance is readily soluble in a mixture of ethyl alcohol and diethyl ether; on allowing the solution to evaporate, the collodion remains behind in the form of a transparent, elastic film. Collodion is used in the manufacture of *celluloid*, which is a mixture (probably a solid solution) of collodion with camphor. The mechanical properties of the resultant celluloid depend on the ratio of the two components. Celluloid is used for the manufacture of all sorts of domestic articles and photographic films.

Other thermoplastic materials are made from cellulose acetate, which has the advantage of being much less inflammable than cellulose nitrates.

Guncotton consists of cellulose trinitrate, the nitrogen content being about 13 %, i.e. practically the theoretical value for the trinitrate. Cellulose trinitrate is an important explosive; when a piece of guncotton is ignited it burns very rapidly with a yellow flame but it does not explode. Explosion can be initiated, however, by mercury fulminate (157). Gaseous products, viz, nitrogen, steam, carbon monoxide and carbon dioxide, are produced in the explosion of nitrocellulose and as the explosion rate is very high guncotton has a violently brisant or high explosive action, unsuitable for firearms but excellent for mines, torpedo heads, etc. When guncotton is treated with solvents like acetone, ethyl acetate, alcohol-ether, it swells up and after evaporating off most of the solvent, a colloidal mass remains behind, which burns more slowly and will explode the original guncotton. These preparations, the explosion velocity of which can be regulated by the method of preparation, form the basis of *smokeless* and *almost smokeless powder*, which is used in large quantities for making ammunition. These explosives frequently contain glycerol trinitrate (112) as well as cellulose trinitrate.

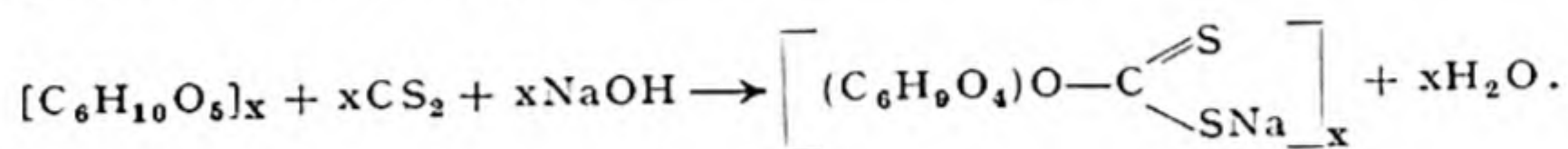
Another application of cellulose nitrates and cellulose acetates is to be found in the manufacture of soluble lacquers. The cellulose derivative is dissolved in appropriate volatile organic solvents. On evaporating the latter from the solution, the cellulose derivative remains behind as a bright clear film, impervious to water.

191. Rayon or artificial silk. In the preparation of artificial fibres from cellulose it is necessary first to convert it into a soluble derivative. The solution is then forced

through a "spinneret" having a number of very fine openings, into the spinning bath, in which the cellulose compound is coagulated as such or the soluble cellulose derivative is decomposed so that regenerated cellulose is precipitated. In either case the colloidal material separates in the form of a bundle of very fine fibres, which are drawn out during the coagulation and spun to form a thicker thread. The thread obtained in this way, has the bright external appearance of natural silk and is used in very large amounts in the textile industries.

The oldest method is that of DE CHARDONNET in which cellulose nitrate dissolved in a mixture of alcohol and ether (collodion) serves as the starting material; the thread obtained from this solution is "denitrated"; the nitro-groups are reduced and the resultant amino-groups split off simultaneously by hydrolysis. This is done by means of a solution of NaSH or NH_4SH . The CHARDONNET process has to a large extent been replaced by better methods.

The *viscose process* (CROSS, BEVAN and BEADLE) is extremely important. By treatment with caustic soda, the cellulose is converted into the so-called alkali cellulose, which is then treated with carbon disulphide, when xanthate esters are produced (compare 154); this can be represented schematically as follows:



This *cellulose xanthate* gives a very viscous colloidal solution (viscose) in dilute caustic soda. By injecting such a solution into an acid bath, e.g. a solution of dilute sulphuric acid and alkali sulphate, the cellulose xanthate is decomposed and cellulose is reprecipitated.

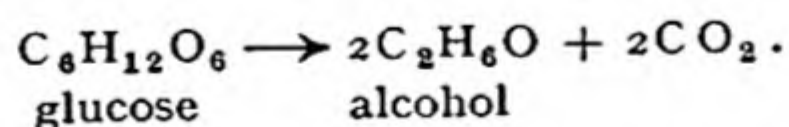
In the *cuprammonium process*, cellulose is dissolved in an ammoniacal solution of copper hydroxide and the solution injected into an acid bath in which the cellulose is regenerated.

Acetate silk is manufactured from cellulose triacetate dissolved in acetone. By injecting the solution into warm air the acetone evaporates and cellulose triacetate separates in the form of a thread.

Alcoholic fermentation

192. Alcoholic fermentation (31) was already known in antiquity, but only in the 19th and 20th centuries has an insight been obtained into the chemical and biochemical reactions taking place.

LAVOISIER established round about 1789, that during fermentation, sugar was broken down into alcohol and carbon dioxide without the addition of water or any other substance. GAY LUSSAC established the equation for this decomposition (1813):

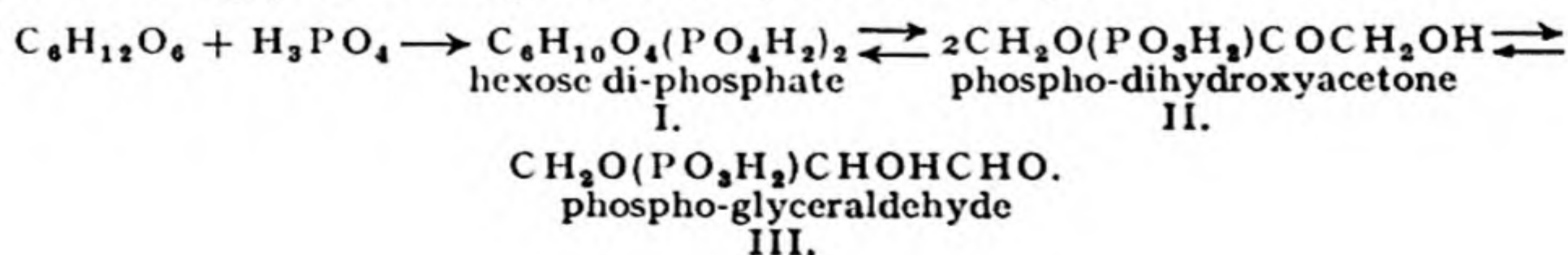


Actually about 95 % of the sugar is recovered in the form of alcohol and carbon dioxide (in equivalent quantities). The question as to the part played by the yeast in this process has been answered in different ways. From obser-

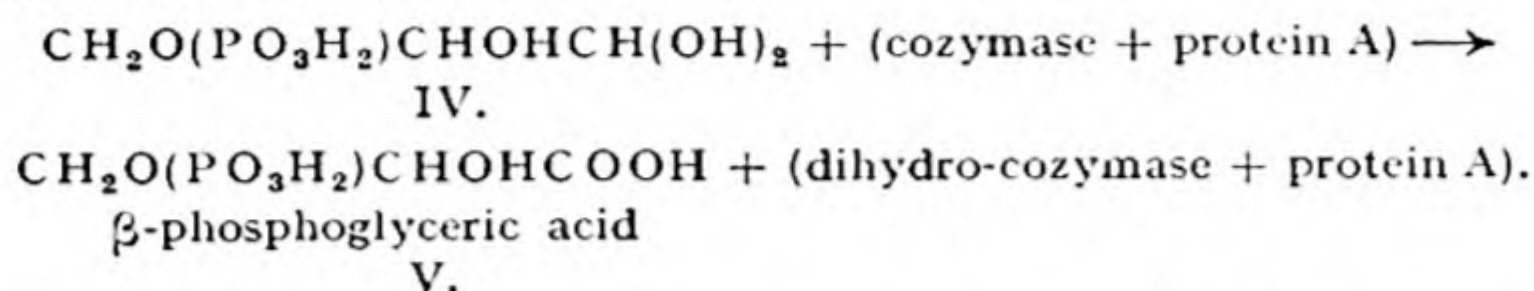
vations by CAGNIARD LATOUR, SCHWANN and KÜTZING (1837) it appeared that yeast belongs to the lower order of plants, from which the conclusion is drawn, that the decomposition of sugars is connected with the vital processes of the yeast cells. This theory was extended and confirmed by the ingenious researches of PASTEUR (1860). He came to the conclusion that fermentation cannot be separated from living and multiplying yeast cells.

In 1897, however, E. BUCHNER showed that fermentation may also occur in the absence of living yeast cells. He ground yeast, which had been dried at a low temperature, with quartz sand and kieselguhr and so ruptured the cell walls so that the semi-liquid cell contents could be soaked up by the kieselguhr. The dough-like mass was then subjected to high pressure when a liquid, the press-juice, was squeezed out and was separated from a few suspended cells, which it still contained, by filtration. This press-juice is able to bring about the fermentation of sugar solution, although this fermentation takes place more slowly than fermentation with an equivalent quantity of yeast. Fermentation is not brought about by live yeast remaining in the press-juice, since the action continues on the addition of an antiseptic like toluene. The fermentation is therefore caused by constituents of the protoplasm of the yeast cells present in the press-juice. It is assumed that a complex of enzymes (207), called *zymase* by BUCHNER, is present in the press-juice, which is able to split glucose into alcohol and carbon dioxide in the presence and with the help of phosphates. This zymase-complex is attached to the protoplasm of the cell; it has not been possible to isolate the individual enzymes from the press-juice.

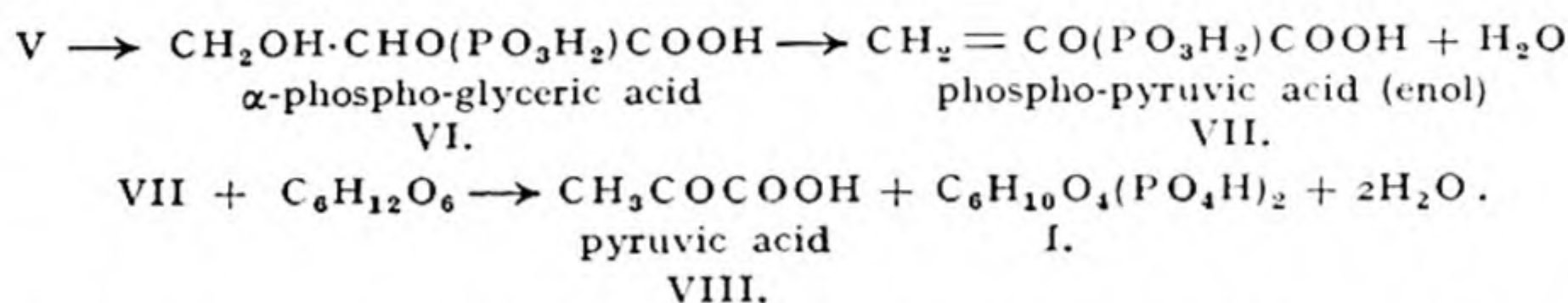
193. When the structure of glucose is compared with that of alcohol and carbon dioxide, it is clear that very drastic alterations must take place in the glucose molecule; actually an oxidation product (CO_2) and a reduction product ($\text{C}_2\text{H}_5\text{OH}$) are produced. It must also be assumed that these substances are formed as a result of a number of rapid reactions, in which various intermediate products will occur. On the basis of investigations by HARDEN and YOUNG, NEUBERG, MEYERHOF, EMBDEN and others the course of alcoholic fermentation can be represented as follows. First of all, by the action of phosphates present in the yeast, a di-phosphate ester, I, is formed from the glucose, which is then split up in the fermenting liquid under the influence of a ferment *hexokinase*, into a mono-phosphate of dihydroxyacetone, II, which in its turn forms an equilibrium with the phosphate ester of glyceraldehyde, III (MEYERHOF):



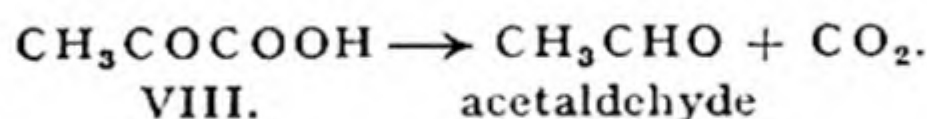
Subsequently the hydrated form of phosphoglyceraldehyde, IV, is dehydrogenated to produce β -phosphoglyceric acid V. This is brought about by a hydrogen carrying ferment, in which the active group, cozymase, is attached to a protein (compare 205 and 351). In this process cozymase takes up two atoms of hydrogen and is converted into *dihydro-cozymase* (VON EULER; WARBURG):



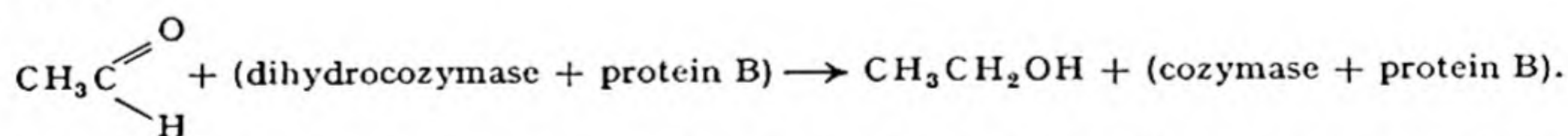
The β -phospho-glyceric acid, V, then passes over into the isomeric α -phosphoglyceric acid, VI, from which the phosphate ester of the enol form of pyruvic acid, VII, is produced by the splitting off of water under the influence of *enolase*:



The ester VII, reacts with glucose with the formation of pyruvic acid, VIII, and glucose diphosphate, I. The pyruvic acid is then decomposed into acetaldehyde and carbon dioxide under the influence of the ferment *carboxylase* (NEUBERG):



The acetaldehyde is reduced to ethanol, the necessary hydrogen being provided by dihydrocozymase, which is converted into cozymase in the process. The dihydrocozymase is again bound up with a protein, which is different from the protein to which cozymase is attached, according to WARBURG.



According to this reaction scheme alcohol and carbon dioxide are produced in equivalent quantities.

A little glycerol, about 3 %, is always found as a by-product in alcoholic fermentation. This may be formed by the reduction of phospho-dihydroxyacetone, II, or of phosphoglyceraldehyde, III, and fission of phosphoric acid, the necessary hydrogen being provided by dihydro-cozymase. When calcium bisulphite is added to a fermenting solution of glucose, the fermentation process is not inhibited but quite different products, namely, acetaldehyde

(as the bisulphite compound) and glycerol in equivalent quantities, as well as carbon dioxide (NEUBERG, CONNSTEIN and LÜDECKE) are produced. Under these conditions the acetaldehyde is fixed as the bisulphite compound and cannot be reduced to alcohol; the formation of glycerol therefore predominates. Alcoholic fermentation is such a complicated process, that the mechanism of the reaction is still not fully established in all its aspects.

Alcoholic fermentation proceeds best at temperatures between 30° and 37° ; too high a concentration of sugar is detrimental for the development of yeast cells. When the alcohol content exceeds 15 %, fermentation stops (with many kinds of yeast this occurs at a lower content). Further, salts containing potassium, magnesium and phosphate must be added as well as nitrogenous substances, which are necessary as food for the yeast cells. A large number of kinds of yeast are known, amongst which there are those which live on the surface of the fermenting liquid (*top yeast*) and others, which collect on the bottom of the vat (*bottom yeast*). Besides glycerol, small amounts of acetaldehyde and acetal are also formed as by-products in alcoholic fermentation. The alcohols in fusel oil (2-methylpropanol-1 and pentanols, see 35), which are produced as by-products in the preparation of alcohol from starch, are not formed from glucose but originate from amino-acids (see 194). Certain kinds of bacteria, which are able to bring about alcoholic fermentation, are also known.

Besides alcoholic fermentation, many other fermentation processes are known, such as the fermentation of milk-sugar to form lactic acid and butyric acid, the formation of butyl alcohol and acetone from starch and that of citric acid from glucose. A number of reactions are grouped together under fermentation processes, in that they take place at temperatures of about 20° to 50° , usually with the evolution of gas and a positive heat effect, and micro-organisms (yeast cells or bacteria) play a part.

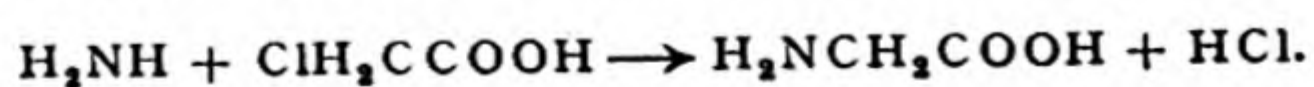
d-Glucose is converted in the animal body under the influence of ferments into *d*-lactic acid. For part of the process the same intermediates are involved as in alcoholic fermentation; the pyruvic acid, however, on account of the absence of carboxylase, is not split up as it is formed into acetaldehyde and carbon dioxide, but is reduced to lactic acid.

(xii) AMINO-ACIDS

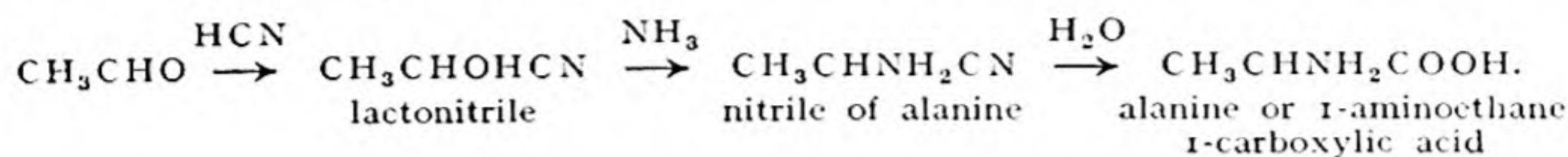
194. Amino-acids are derivatives of alkane carboxylic acids, in which one or more atoms of hydrogen in the alkyl group are replaced by NH_2 . They form an important class of compounds, since various amino-acids are obtained as fission products of proteins; at least twenty four amino-acids of known structure have been found in such products. Some amino-acids or their amides occur in the free state in the vegetable kingdom.

Mono-amino-acids can be prepared in various ways.

1st By the action of ammonia on halogeno-fatty acids (129):



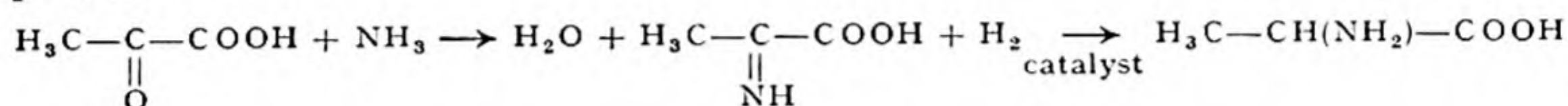
2nd A good preparative method for *1-amino-acids* (α -amino-acids) consists of allowing alcoholic ammonia to react with aldehyde cyanhydrins (59) and subsequent hydrolysis of the resultant amino-nitrile (STRECKER):



3rd Starting from ketonic acids (147), these may be converted into their oximes or hydrazones, which are then reduced, *e.g.*:

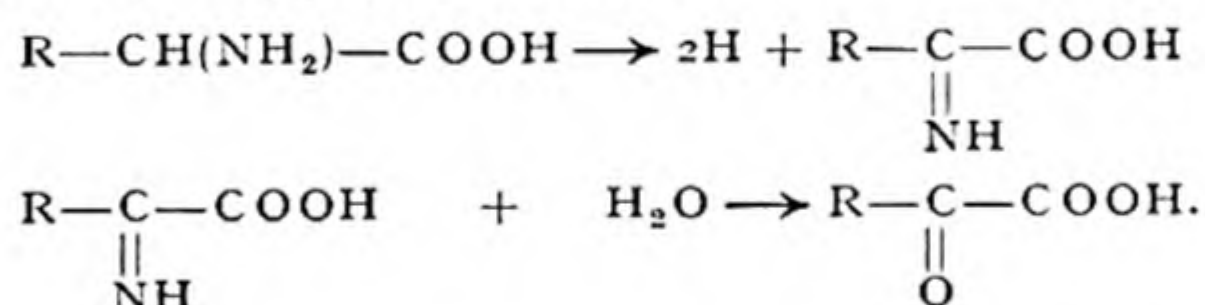


1-Amino-acids may be obtained directly from 1-keto-acids by reducing a mixture of ketonic acid (as ammonium salt) and ammonia with hydrogen with the aid of a palladium catalyst (KNOOP). A *ketimido-acid* is probably produced as an intermediate product:

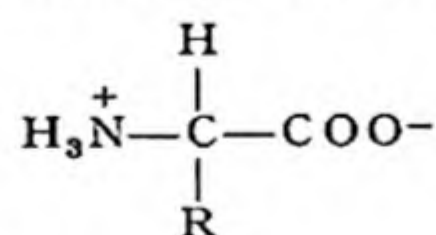


This reaction can also occur under the catalytic action of certain enzymes.

Conversely, 1-amino-acids may be oxidised by oxygen to keto-acids via imino-acids formed as intermediates. This reaction takes place in the presence of dehydrogenation ferments (*dehydrases*, compare 351), which occur in the liver and in the kidneys (KREBS); the hydrogen, which is split off, is taken up by a reduceable co-enzyme and is eventually oxidised by oxygen to water:



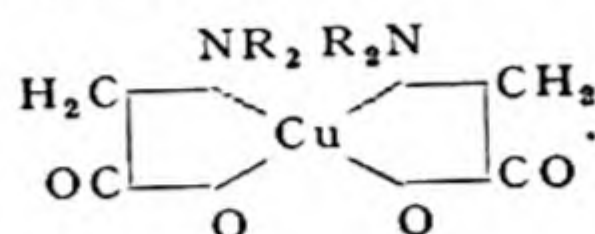
The amino-acids are well defined crystalline compounds; the majority are readily soluble in water, sparingly soluble in alcohol and insoluble in apolar organic solvents. From investigations on the dissociation constants it appears that in aqueous solution an amino-acid is present chiefly in the form of amphoteric ions (BJERRUM), as shown below:



In these ions the positive charge on the nitrogen atom and the negative charge on the COO^- group are separated by the grouping $\text{H}-\underset{|}{\text{C}}-\text{R}$. Also in the solid state it is accepted that the amino-acids have the structure of internal salts; the solubilities of the amino-acids are in agreement with

this suggestion as well as the high melting points of these compounds and the fact that they cannot be distilled without undergoing decomposition.

The 1- and 2-amino-acids give well defined, crystalline copper salts, which are intensely blue in colour and sparingly soluble in water. These salts are only very slightly dissociated in aqueous solution; a precipitate of copper sulphide is produced with hydrogen sulphide, but most of the other reactions for copper ions remain negative. Cupric oxide is slowly formed on boiling with alkalis. It is assumed therefore, that the copper is combined in the form of a complex, *i.e.* with two heteropolar bonds to the COO^- groupings and with two coordinate bonds to the nitrogen atoms:

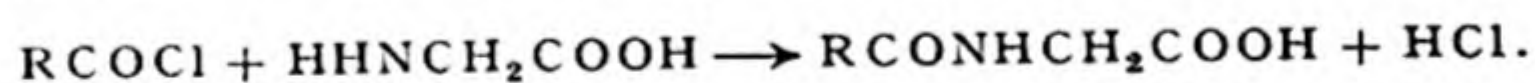


The possibility that the copper may have replaced a hydrogen atom of one of the NH_2 groups, is excluded, because dialkylamino-acids of the type $(\text{R})_2\text{NCH}_2\text{COOH}$, also give complex copper salts.

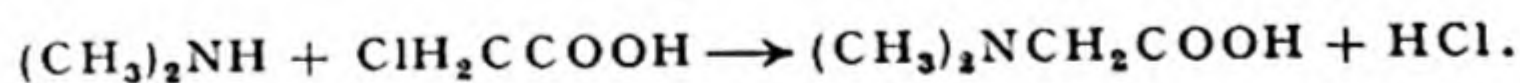
Various amino-acids give double compounds with metal salts like calcium chloride, which gives $\text{CaCl}_2\text{H}_2\text{NCH}_2\text{COOH} \cdot 3\text{H}_2\text{O}$ with glycine. Many 1-amino-acids give an intense red colour when an aqueous solution is treated with ferric chloride.

Amino-acids can be esterified by passing hydrogen chloride into an alcoholic solution; the hydrochlorides of the esters, *e.g.* $\text{Cl}(\text{H}_3\text{N})\text{CH}_2\text{COOC}_2\text{H}_5$, separate. These esters have basic properties, since they contain no free carboxyl groups. The esters can be obtained from the hydrochlorides by treating the latter at low temperatures with caustic potash solution and immediately extracting with ether. The esters of the amino-acids can be distilled in a vacuum without decomposition.

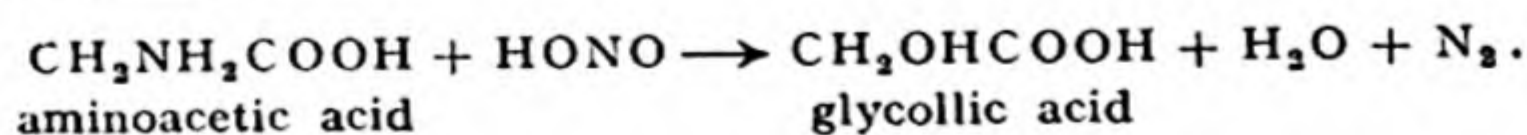
Various substituents can be introduced into the amino-group of the amino-acids. One of the atoms of hydrogen is replaced by an acid radical by the action of acid chlorides, with the production of a substituted amide:



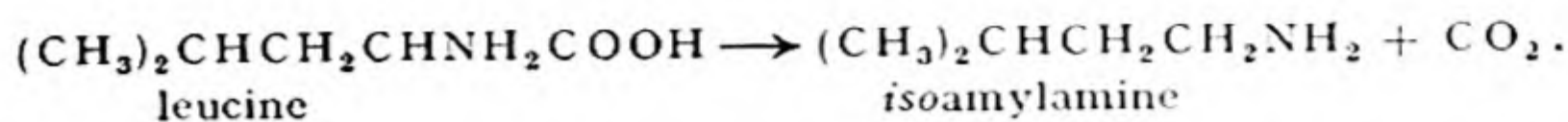
Amino-acids are also known in which the hydrogen of the amino-group is replaced by alkyl. These acids can be prepared by the action of amines on halogeno-acids:



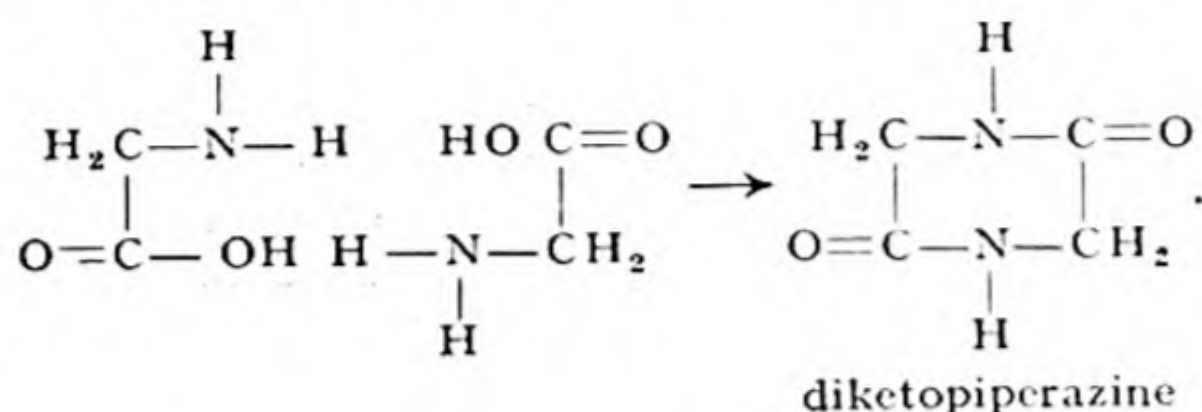
Hydroxy-acids (**130**) are produced by the action of nitrous acid on unsubstituted amino-acids:



On careful heating in high boiling solvents some amino-acids split off carbon dioxide and are converted into amines:

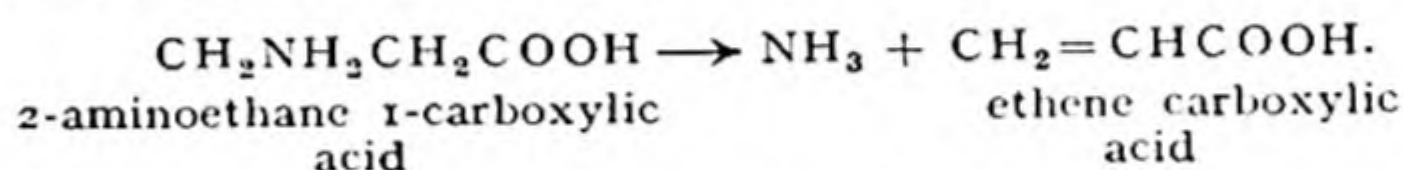


The 1-, 2- and 3-amino-acids show a similarity to the 1-, 2- and 3-hydroxy-acids in the following reactions. The 1-amino-acids (α -amino-acids) easily give anhydrides (amides) by the fission of two molecules of water from two molecules of acid (CURTIUS). These compounds are called *diketopiperazines*:

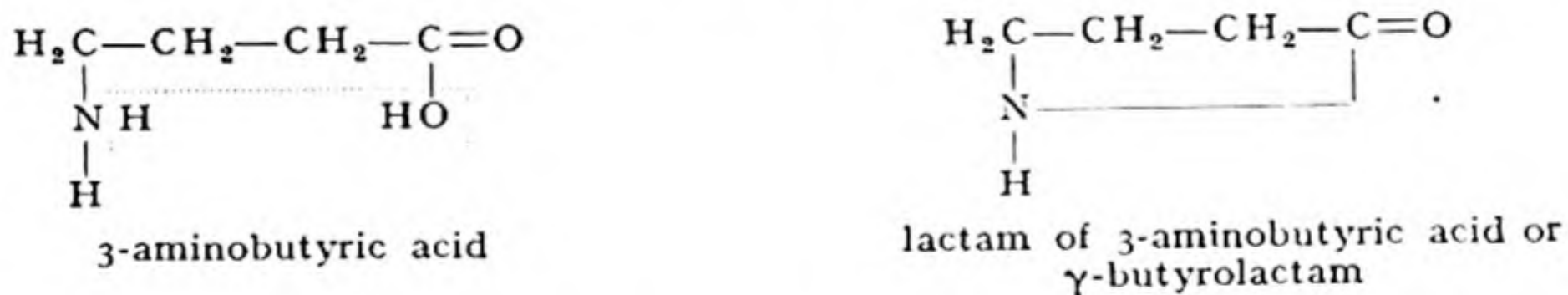


They may also be formed from esters of 1-amino-acids, when two molecules of alcohol are split off.

The 2-amino-acids (β -amino-acids) can split off ammonia with the formation of unsaturated acids (99):



The 3-amino-acids (γ -amino-acids), like the 3-hydroxy-acids give internal anhydrides, which are called *lactams* by analogy with the lactones:

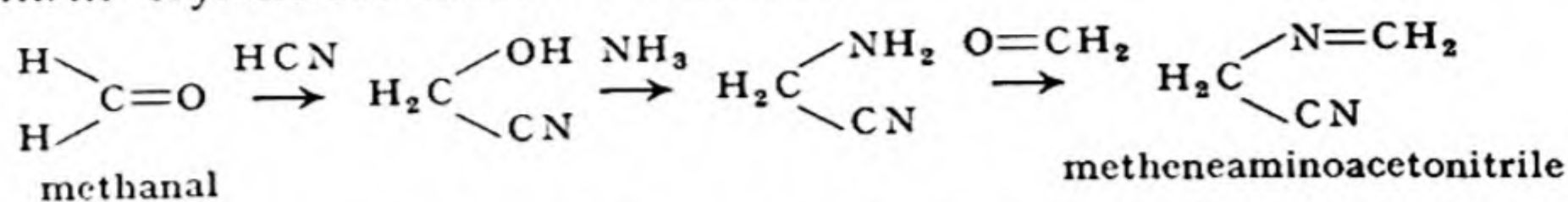


All the amino-acids found among the fission products of proteins are 1-amino-acids. This group of acids therefore is discussed in more detail. All the 1-amino-acids except aminoacetic acid have an asymmetric carbon atom in the molecule. Diamino-acids, monoamino-dicarboxylic acids, hydroxy-amino-acids, amino-acids containing sulphur and amino-acids substituted by cyclic groups of atoms, are also found amongst the fission products of proteins.

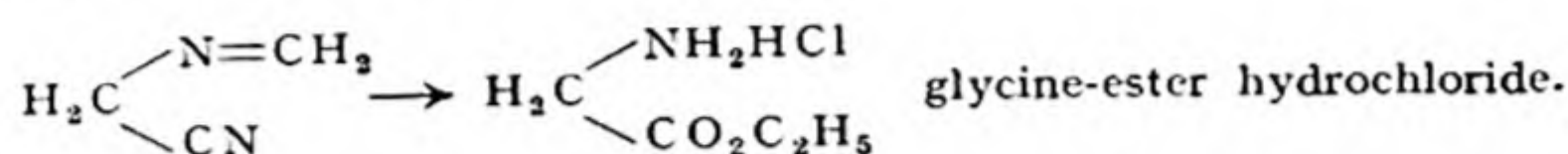
Mono-amino-monocarboxylic acids

195. *Aminoacetic acid, aminomethane carboxylic acid, glycine, glycoll* $\text{NH}_2\text{CH}_2\text{COOH}$, was observed by BRACONNOT as early as 1820 as a fission product of animal gelatine (glue) by boiling with baryta water. Glycine is produced by the hydrolysis of many proteins particularly gelatine ($\gamma\lambda\upsilon\chi\omicron\sigma$ = sweet, $\kappa\omicron\lambda\lambda\eta$ = glue).

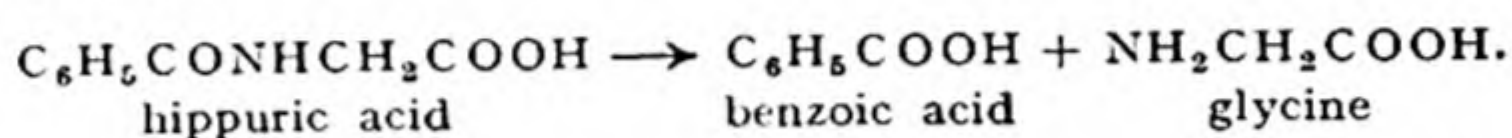
Glycine can be prepared as follows (KLAGES). Methanal, ammonium chloride and potassium cyanide are brought together in cold aqueous solution, when *metheneaminoacetonitrile* crystallises from the solution:



By boiling with alcoholic hydrochloric acid, hydrolysis takes place with the splitting off of ammonia and methanal and subsequent esterification, by which the hydrochloride of glycine-ester is produced:

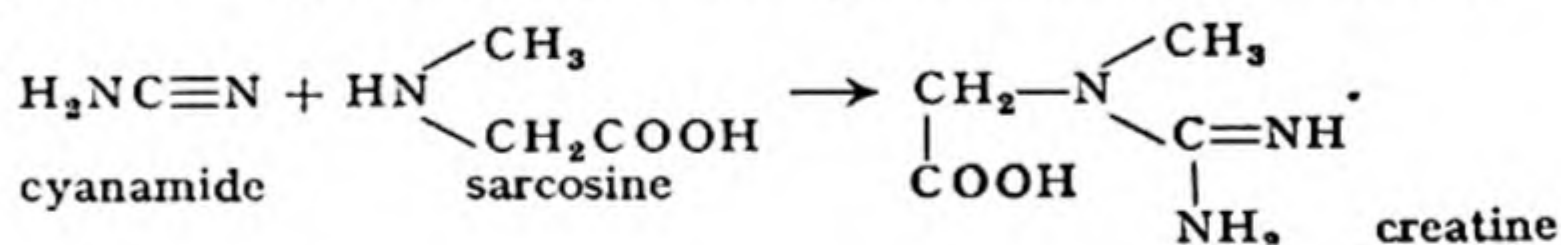


Hippuric acid, a substance, which occurs in the urine of herbivorous animals (horses), on boiling with dilute acids takes up a molecule of water, like all acid amides, and is converted into glycine and benzoic acid:

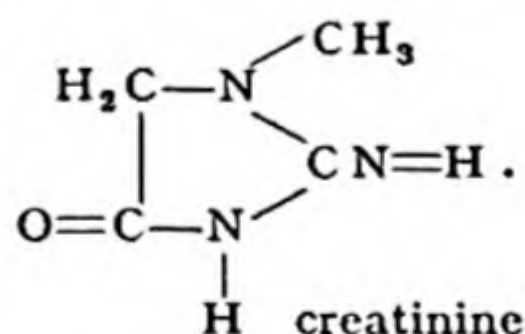


Benzoic acid is formed during the metabolism of constituents of herbivorous food and also by the action of intestinal bacteria on phenylalanine, which is a structural unit of proteins. The benzoic acid is made innocuous in the organism by forming the benzoyl derivative of glycine, hippuric acid. Hippuric acid also occurs in small quantities in human urine. It can be obtained synthetically by the action of benzoyl chloride on glycine.

The mono-methyl derivative of glycine, *sarcosine* $\text{H}_3\text{CNHCH}_2\text{COOH}$, is a degradation product of *creatine*, a substance, which occurs in the form of a compound with phosphoric acid, to the extent of about 0.3 % in muscle fibre. Creatine is a guanidine derivative (153). It may be prepared synthetically from cyanamide and sarcosine:

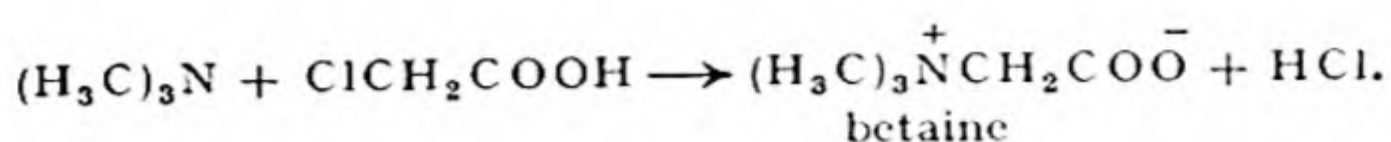


By splitting off a molecule of water from creatine, *creatinine*, which occurs in urine, is produced:



Betaine $\text{C}_5\text{H}_{11}\text{O}_2\text{N}$, occurs in many plants, e.g. in beetroot juice and therefore in molasses; it crystallises with 1 mol. of water and melts, when anhydrous, at 293° ; it is a very stable compound.

The structure of betaine follows from its formation by the addition of trimethylamine to mono-chloroacetic acid with the removal of hydrogenchloride. The molecule of betaine may be regarded as an amphoteric ion:



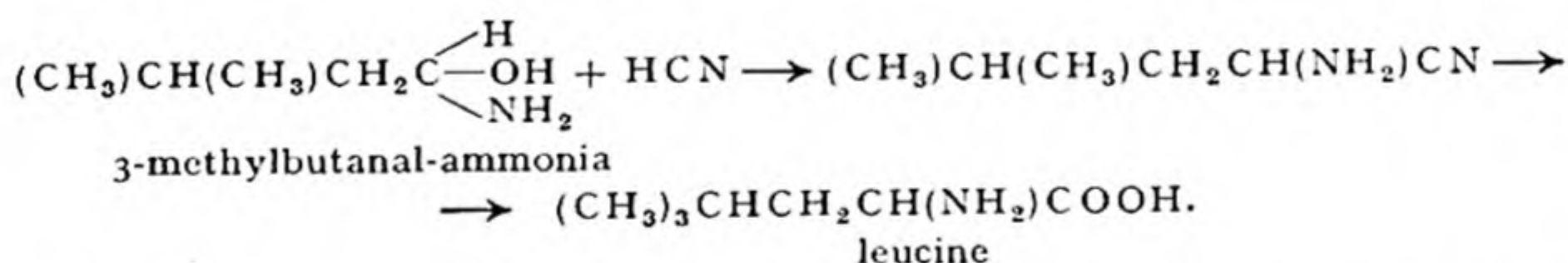
In the betaine molecule, the formation of an internal salt, as occurs also with other amino-acids, can be recognised.

Other tertiary amines containing a carboxyl group, also, can form internal ammonium salts, which are generally called betaines. In accordance with their salt-like character, betaines are readily soluble in water, insoluble in apolar organic solvents and have high melting points.

l-Aminopropionic acid, *dl*-alanine, $\text{CH}_3\text{CH}(\text{NH}_2)\text{COOH}$, can be made from *l*-chloropropionic acid and ammonia or from acetaldehyde (63). *l*-Alanine is a fission product of proteins.

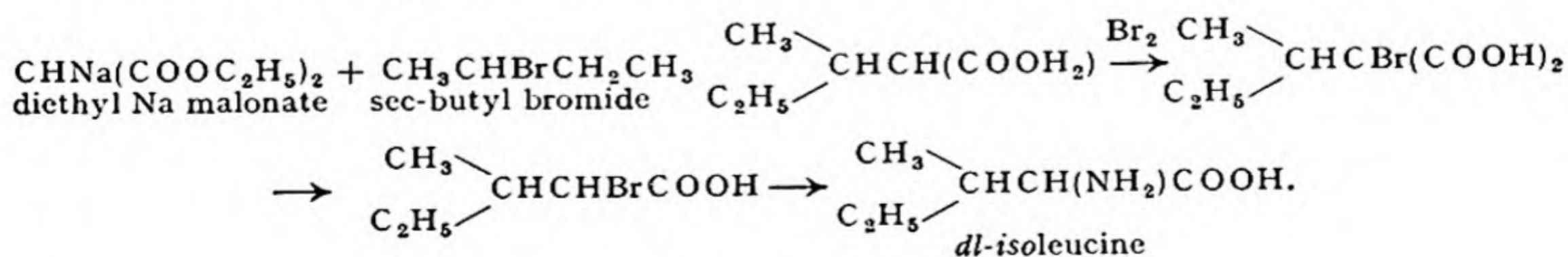
2-Methyl-*l*-aminopropane *l*-carboxylic acid, *l*-amino-isovaleric acid or *valine*, $(\text{CH}_3)_2\text{CHCH}(\text{NH}_2)\text{COOH}$, can be prepared from *l*-bromo-isovaleric acid and ammonia. Optically active valine occurs in the free state in germinating lupin seeds and is also found in small quantities in the hydrolysis products of proteins.

3-Methyl-*l*-aminobutane *l*-carboxylic acid, *leucine*, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{NH}_2)\text{COOH}$, is an important fission product from proteins. PROUST and BRACONNOT (1820) observed that this substance is formed by the decomposition of cheese or meat. Leucine also occurs in germinating seeds; *dl*-leucine can be prepared by the action of hydrocyanic acid on 3-methylbutanal-ammonia and hydrolysis of the resultant nitrile:



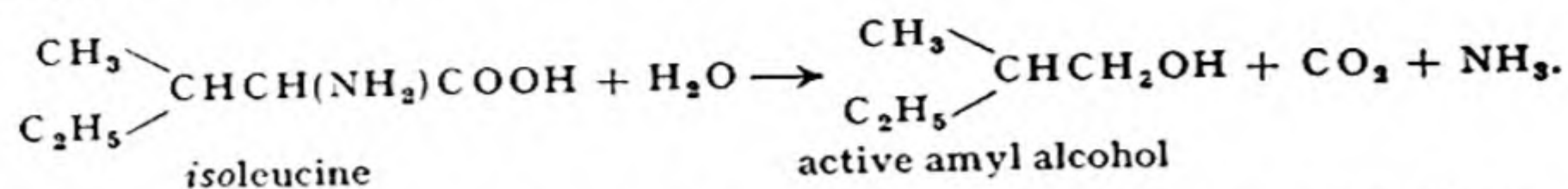
2-Methyl-*l*-aminobutane *l*-carboxylic acid or *isoleucine*, $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{NH}_2)\text{COOH}$, occurs along with leucine in molasses and in the germinating seeds of *vicia sativae* and has also been observed as a fission product of proteins.

The structure is apparent from the following synthesis (F. EHRLICH):



Isoleucine contains two asymmetric carbon atoms.

Leucine, *isoleucine* and *valine* can be split up by yeasts according to the equation:



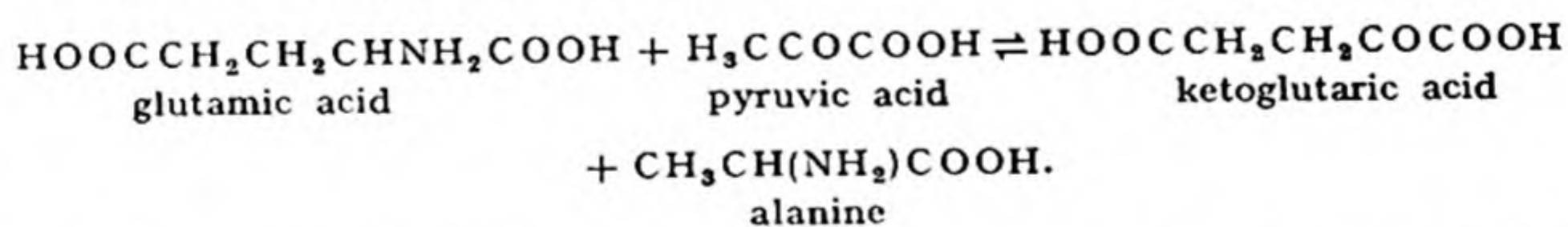
The alcohols, which occur in fusel oil (31, 35), are produced in accordance with this reaction (F. EHRLICH) by the action of yeast on the above mentioned amino-acids, the latter being formed from proteins which are present in the material (grain, potatoes) used for the preparation of alcohol.

Mono-amino-dicarboxylic acids

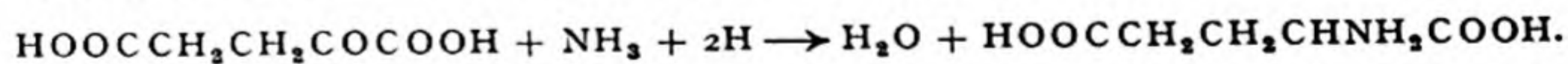
196. *1-Aminoethane 1,2-dicarboxylic acid, aminosuccinic acid or aspartic acid*, $\text{COOHCH}(\text{NH}_2)\text{CH}_2\text{COOH}$, is found as a fission product of proteins. The structure is apparent from its formation from bromosuccinic acid and ammonia and from the formation of malic acid by the action of nitrous acid on aspartic acid. A mono-amide of aminosuccinic acid, *asparagine*, $\text{H}_2\text{NCOCH}_2\text{CH}(\text{NH}_2)\text{COOH}$, occurs in the laevo-rotatory form in germinating seeds, e.g. of lupins and also in asparagus; *l*-asparagine is tasteless, *d*-asparagine tastes sweet.

1-Aminopropane 1,3-dicarboxylic acid, aminoglutaric acid or glutamic acid, $\text{COOHCH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{COOH}$, is also produced by the hydrolysis of albumin. The mono-amide of this acid, *glutamine*, occurs in the vegetable kingdom, especially in germinating seeds. Asparagine and glutamine are found as fission products of some proteins on enzymatic degradation.

Under the influence of certain enzymes occurring in many animal tissues and also in plants and in micro-organisms, a remarkable reaction can take place between *l*(+)-glutamic acid and pyruvic acid (or another 1-keto-acid). As a result, the ketonic acid is converted into a 1-amino-acid, while keto-glutaric acid is produced from the glutamic acid; the reaction is reversible (BRAUNSTEIN and KRITZMANN):



On the other hand, glutamic acid can be produced again from ketoglutaric acid in the way described on p. 299; according to VON EULER, enzymes, which bring about this formation of glutamic acid, are present in many animal tissues:

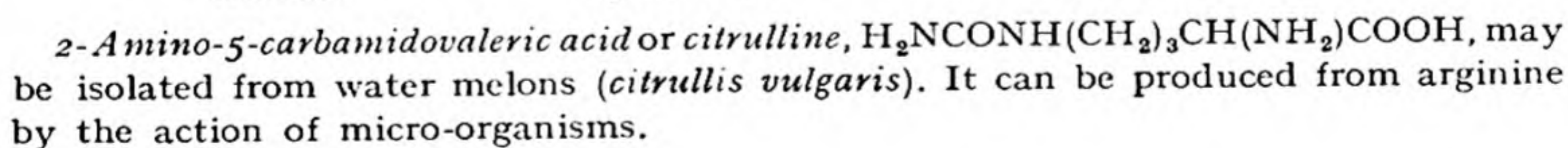
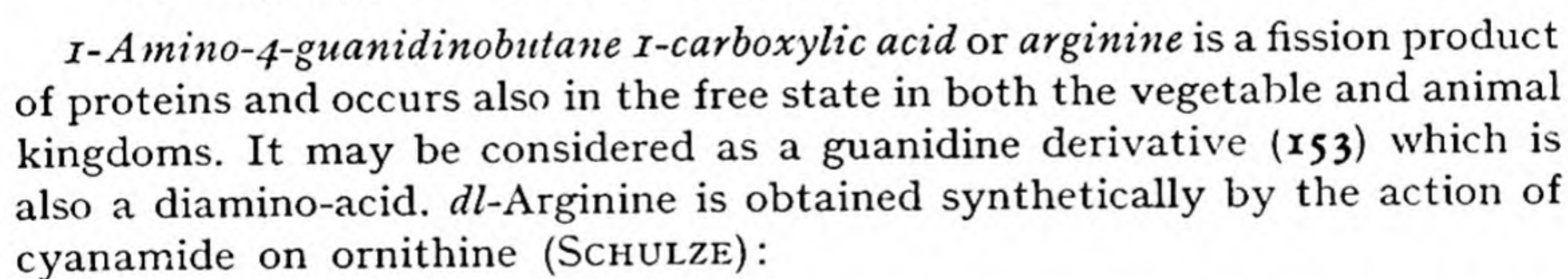


Glutamic acid can therefore serve as an intermediate product in the biochemical synthesis of amino-acids.

Diamino-mono-carboxylic acids

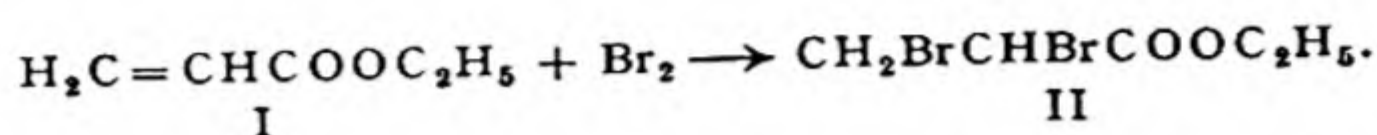
197. *1,4-Diaminobutane 1-carboxylic acid or ornithine*, $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$, and *1,5-diaminopentane 1-carboxylic acid or lysine* are both

The synthesis of lysine is carried out as follows (E. FISCHER). Sodium ethyl malonate is treated with *3-chloropropane 1-carbonitrile* when *diethyl 4-cyanobutane 1,1-dicarboxylate* is produced, which is converted into the sodium salt of an oxime, with the liberation of carbon dioxide and alcohol, by treatment with ethyl nitrite and sodium alcoholate. The NOH-group is reduced to NH_2 and the cyano-group to CH_2NH_2 by the action of sodium and alcohol with the production of optically inactive lysine:

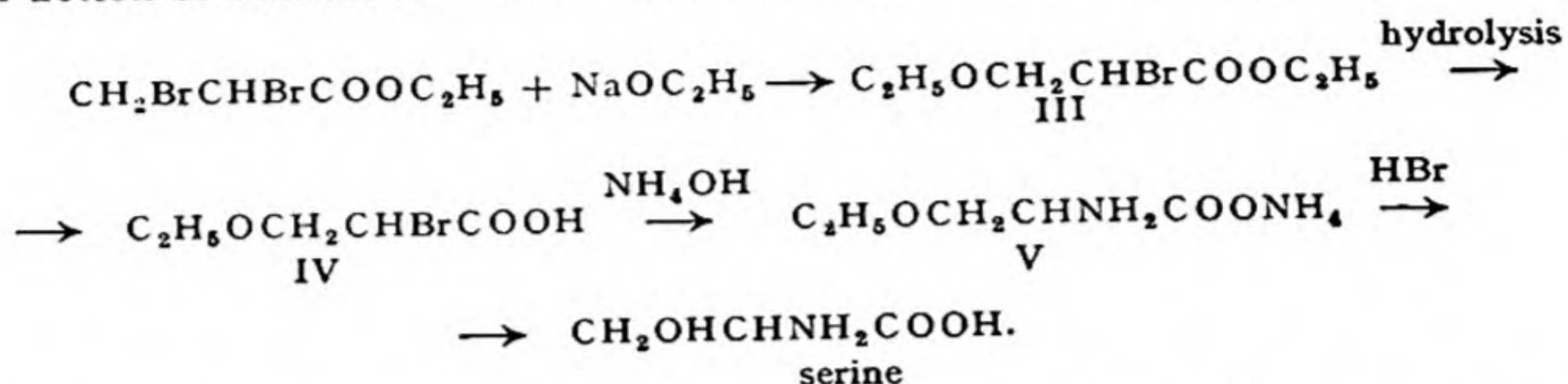


198. *2-Hydroxy-1-aminopropionic acid* or *serine*, $\text{HOCH}_2\text{CH}(\text{NH}_2)\text{COOH}$, is produced by the hydrolysis of proteins, particularly *sericin*, a constituent of natural silk. The structure of serine follows from its conversion into glyceric acid $\text{CH}_2\text{OHCHOHCOOH}$ by the action of nitrous acid, from its conversion into alanine by reduction with hydriodic acid and from its synthesis from glycolaldehyde CH_2OHCHO with hydrocyanic acid and ammonia.

dl-Serine can be prepared by treating ethyl acrylate, I, (WOOD and DU VIGNEAUD) with bromine when ethyl dibromoacrylate, II, is produced:



By the action of sodium ethoxide on II, the terminal Br-atom is replaced by OC₂H₅:



III is hydrolysed to the corresponding acid, IV, in which the bromine atom is replaced by NH₂ (V) by the action of ammonia; serine is produced by treatment of V with hydrobromic acid.

1-Amino-2-hydroxybutyric acid or *d(-)-threonine*, CH₃CH(OH)CH(NH₂)-COOH, a homologue of serine, is a fission product from many proteins (ROSE, 1934); it gives 1-aminobutyric acid on reduction with hydriodic acid. The structure of this amino-acid has been proved by synthesis. It is called *threonine* because the spatial configuration of the form occurring in nature is similar to that of *d(-)-threose* (163).

Cysteine HSCH₂CHNH₂COOH, is an example of an amino-acid containing also a thiol grouping. The structure follows, for example, from its relationship with serine, from which cysteine is obtained by heating with phosphorus penta-sulphide. Cysteine is easily converted into cystine, HOOC-CHNH₂CH₂S—SCH₂CHNH₂COOH, by atmospheric oxidation.

Cystine, C₆H₁₂O₄N₂S₂, was observed by WOLLASTON as early as 1810 as a constituent of bladder stones, hence the name (κυστις = bladder). Cystine is very sparingly soluble in cold water but readily soluble in alkalis; it is produced in appreciable quantity by the hydrolysis of keratin (see 201). Cysteine is produced from cystine by reduction with tin and hydrochloric acid.

This reduction may also be brought about by putrifying bacteria; the cysteine so produced may be reduced by them still further with the production of hydrogen sulphide.

Methionine CH₃SCH₂CH₂CH(NH₂)COOH, also is a sulphur containing amino-acid found as a degradation product of proteins.

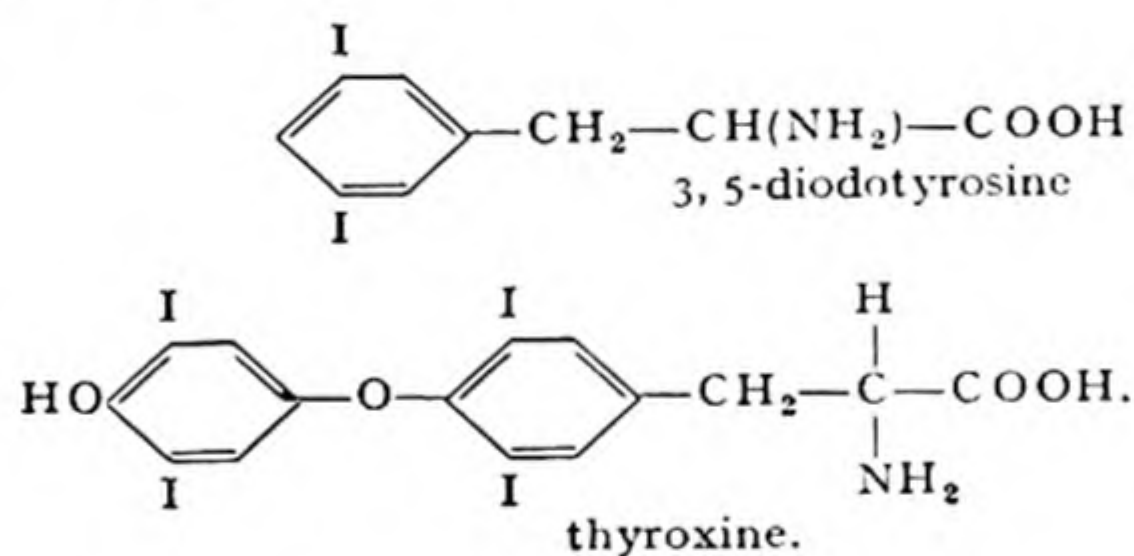
It stimulates the growth of rats fed on a diet deficient in cystine. Methionine is converted into cystine biochemically. This is demonstrated by feeding rats with methionine containing radioactive sulphur, when the latter is recovered in radioactive cystine derived from tissue proteins.

Amino-acids with cyclic groups of atoms

199. *2-Phenyl-1-aminopropionic acid* or *phenylalanine*, $C_6H_5CH_2CH(NH_2)COOH$, is one of the fission products of fibroin, a protein occurring in silk.

2-(p-Hydroxyphenyl)-1-aminopropionic acid, *hydroxyphenylalanine* or *tyrosine*, $HOC_6H_4CH_2CH(NH_2)COOH$, was first observed as a decomposition product of cheese (*τυρός*). It is produced also in the hydrolysis of many other proteins. It occurs in the free state in the vegetable kingdom. Diiodotyrosine, an amino-acid containing iodine, is a degradation product of proteins from the thyroid gland.

An amino-acid, which contains iodine, 3,5-diiodotyrosine or *iodogorgonic acid*, was first isolated from the hydrolysis products of *gorgine*, a constituent of a coral (*Gorgonia carolinii*) and is prepared by the iodination of tyrosine in alkaline media. *1-Thyroxine* $C_{15}H_{11}O_4NI_4$, is obtained by the enzymatic hydrolysis of the protein in the thyroid gland; this amino-acid is the active gland hormone (307). By careful catalytic reduction of thyroxine, the iodine atoms may be replaced by atoms of hydrogen with the production of *thyronine*, $C_{15}H_{15}O_4N$, which affords *p*-hydroxybenzoic acid (263), quinol (232), oxalic acid (122) and ammonia, when fused with potash. The structure of thyroxine derived from these data has been confirmed by synthesis (KENDALL; HARRINGTON):

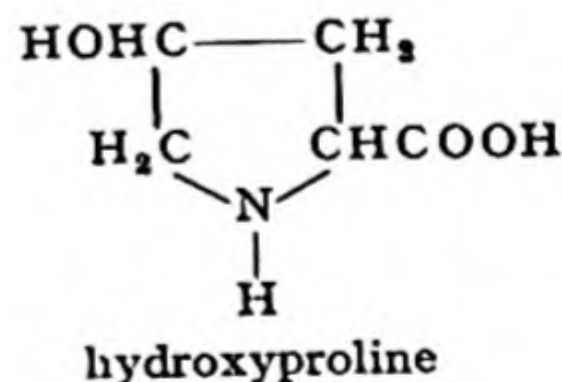
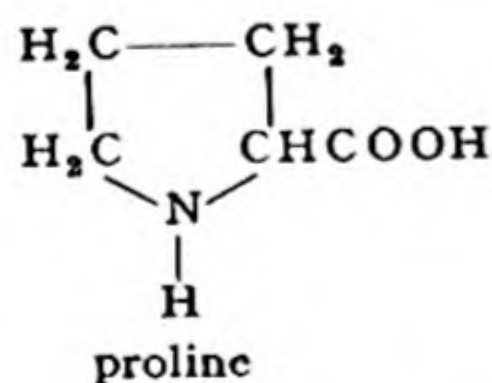
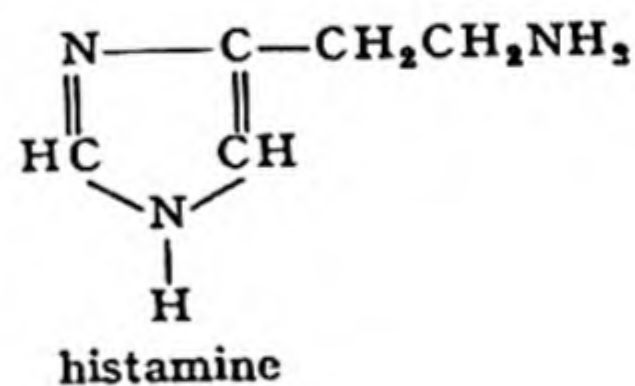
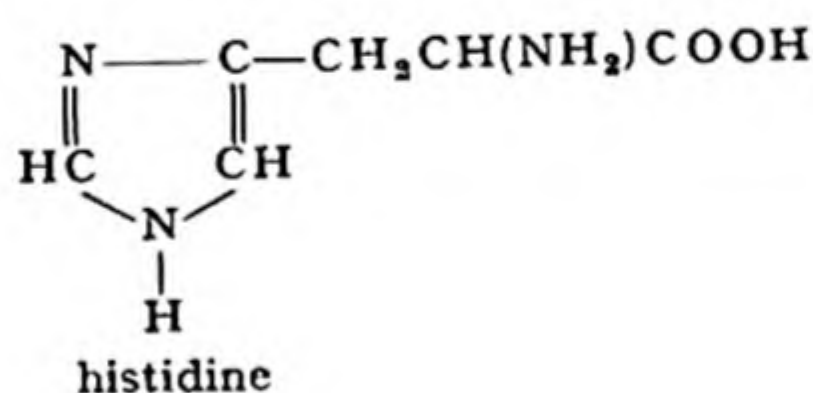
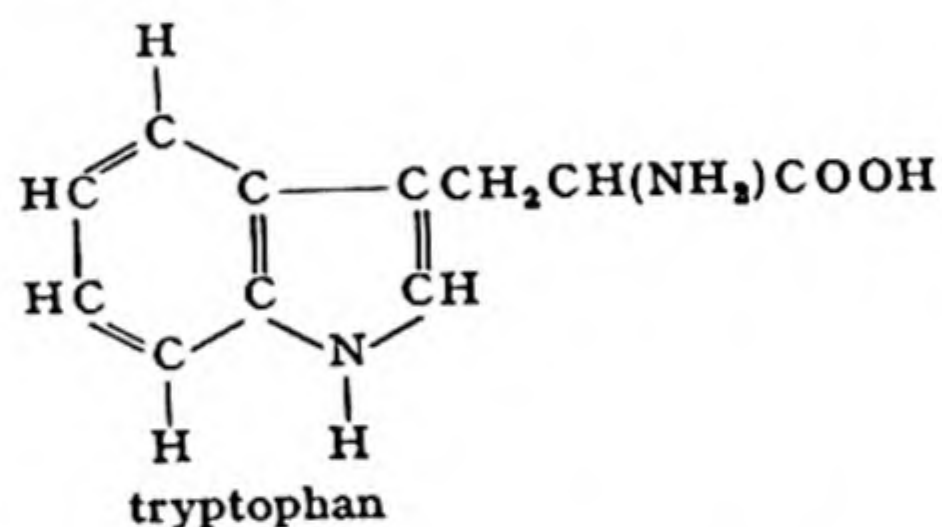
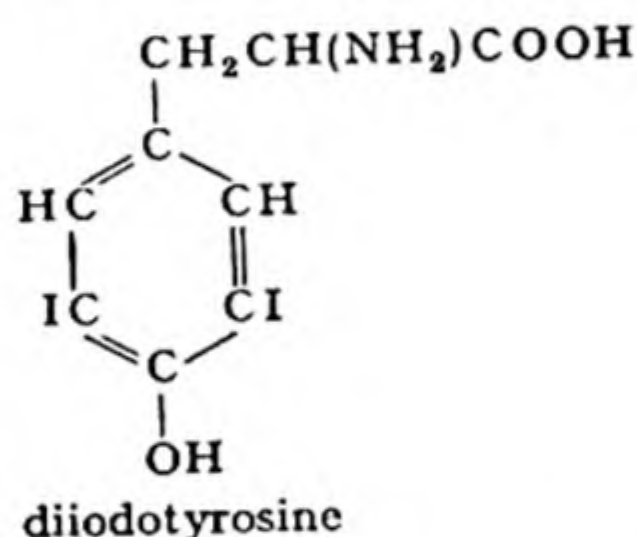
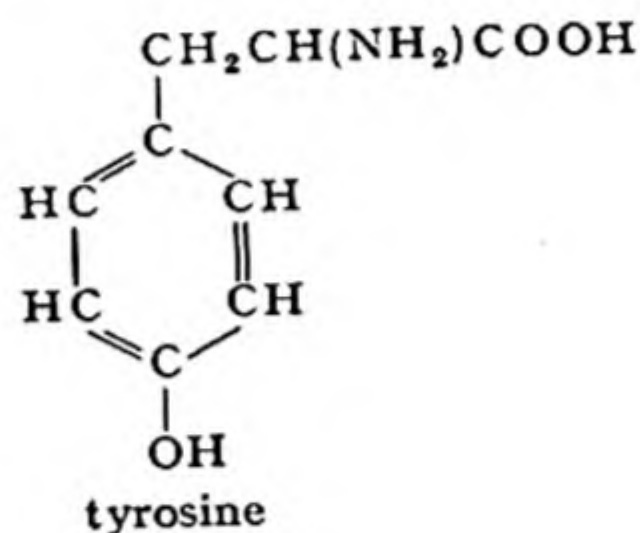
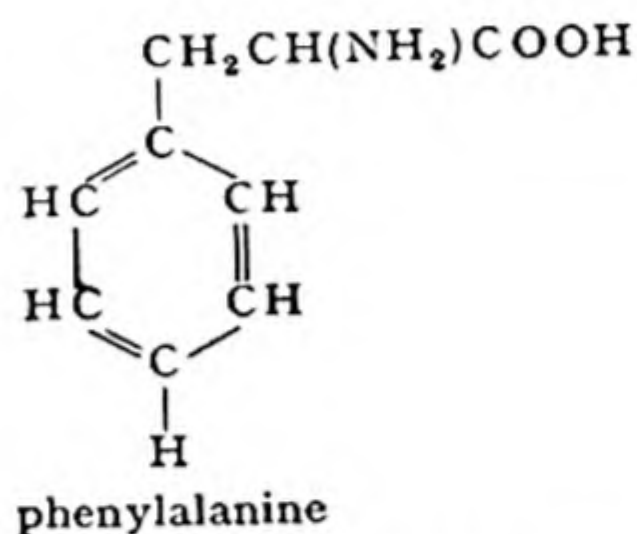


2-Indolyl-1-aminopropionic acid or *tryptophan*. Tryptophan was first observed amongst the products obtained in the enzymatic hydrolysis of proteins. Free tryptophan gives a violet colouration with bromine water and also gives the reaction described in 200. Since tryptophan is decomposed on warming with mineral acids, it is not detected in the hydrolysis products of proteins by acids. It is a derivative of indole (315).

2-Iminazolyl-1-aminopropionic acid or *histidine* is found amongst the fission products of various proteins and occurs in the free state in both the animal and vegetable kingdoms. It is a derivative of glyoxaline (see 323). By the action of putrifying bacteria, carbon dioxide is split off from histidine with the formation of *histamine*, which exerts a powerful action in increasing the blood-pressure and is therefore used in medicine.

Phenylalanine, tyrosine, tryptophan and histidine are to be regarded as derivatives of alanine in which one of the hydrogen atoms of the methyl group is replaced by a cyclic nucleus.

Pyrrolidine 2-carboxylic acid or *proline*, $C_4H_7(NH)COOH$ and *hydroxyproline*, $C_4H_6(NH)(OH)COOH$, are both pyrrolidine derivatives (see 314). They do not belong to the amino-acids since they do not contain an amino-group. Their basic properties are to be ascribed to the cyclic imino-groups. They are mentioned here because they are important fission products of animal proteins.



The melting points and specific rotations of a number of amino-acids are given in Table 36. For those forms of alanine, leucine, aspartic acid, glutamic acid, lysine, ornithine, cysteine, proline and tyrosine, which are found as degradation products of proteins, it has been proved by either synthesis or degradation that they are related to naturally occurring laevo-rotatory serine, which is designated *l*(-)-serine. Therefore all the above-mentioned

amino-acids belong to the *l*-series. Amino-acids derived from proteins from cancerous tumours are an exception. According to researches by KÖGL, these amino-acids, especially glutamic acid, occur in these tumours in the *d*-form.

TABLE 36
MELTING POINTS AND SPECIFIC ROTATIONS OF SOME AMINO-ACIDS

Some amino-acids occurring in nature	Melting or decomposition point	α_D
Glycine	$\approx 240^\circ$ (decomp.)	Inactive
<i>l</i> (+)-Alanine	297°	+ 2.7°
<i>l</i> (—)-Serine	228° (decomp.)	— 6.8°
<i>d</i> (—)-Threonine	$255-257^\circ$ (decomp.)	— 28°
<i>l</i> (—)-Cystine	$258-261^\circ$ (decomp.)	— 222°
<i>l</i> (+)-Valine	315°	+ 6.4°
<i>l</i> (—)-Leucine	295°	— 10.4°
Isoleucine	280°	+ 9.7°
<i>l</i> (—)-Phenylalanine	$\approx 278^\circ$	— 35.3°
<i>l</i> (—)-Tyrosine	$342-344^\circ$	— 8.6° (in 21 % HCl)
Tryptophan	$\approx 289^\circ$	— $30-34^\circ$
Histidine	$\approx 277^\circ$	— 39.7°
<i>l</i> (+)-Arginine	238° (decomp.)	+ 26.5°
<i>k</i> (+)-Ornithine	—	+ 16.8° (in HCl)
<i>l</i> (+)-Lysine	224°	+ 15.3°
<i>l</i> (—)-Aspartic acid	270°	+ 6° (21.5°) <i>l</i> -rotatory at higher temps.
<i>l</i> (—)-Asparagine	$226-227^\circ$	— 5.4°
<i>l</i> (+)-Glutamic acid	206°	+ 12.0°
<i>l</i> (+)-Glutamine	256° (<i>d.l.</i> form)	+ 6.4°
<i>l</i> (—)-Proline	$215-220^\circ$	— 82.0°
Hydroxyproline	$\approx 270^\circ$	— 80.0°

(xiii) PROTEINS

200. Apart from fats and mineral constituents the dry matter from the animal body consists for the greater part of proteins. Proteins also occur in all living plant cells. Along with fats and carbohydrates they form the most important constituents of food.

The name proteins was introduced in 1839 by G. J. MULDER, because he thought that all albuminous substances were derived from one basic type ($\pi\rho\omega\tau\epsilon\rho\omicron\varsigma$ = the first).

There are very many different proteins; they have colloidal properties, which makes their purification and separation very difficult. In addition, the difference between the different kinds is frequently not very well defined,

so that it is difficult to determine whether a protein preparation consists of molecules of the same kind or of molecules of different kinds. A number of proteins have been obtained in a crystalline form, including *haemoglobin*, various enzymes, which must be regarded as belonging to the proteins, and some vegetable albuminoid substances.

Proteins have very high molecular weights. Since they decompose on heating they show no definite melting point and they cannot be distilled. The percentage compositions of the various kinds of proteins do not differ greatly and lie between the following limits; in which the small quantities of inorganic salts, which occur in admixture with natural proteins, are neglected:

Carbon 52.4–54.5 %, oxygen 21–23.5 %, hydrogen 6.9–7.3 %, sulphur 0.8–2 %, nitrogen 15.5–18 %.

Most proteins have the properties of hydrophilic colloids; they can be precipitated from sols in two ways, namely, reversibly or irreversibly. The proteins are reversibly precipitated by adding a concentrated solution of sodium chloride, magnesium or ammonium sulphate or similar neutral salts. As the concentration of ammonium sulphate necessary for this purpose is different for different proteins, use can be made of this fact to bring about a rough separation; also the hydrogen ion concentration in the solution (p_H) has an influence on the flocculation of a protein. The flocculated protein still possesses the same properties as before precipitation. Also most albuminoid substances are precipitated unchanged by adding alcohol or acetone to an aqueous solution. The colloidal, soluble proteins have the properties of amphoteric electrolytes.

By the action of strong alcohol or acetic acid, the proteins are converted into the *coagulated state*. This coagulation also occurs on heating proteins to 100° or by boiling with water or by adding concentrated nitric acid to the aqueous solution.

The coagulated albumins are insoluble in water; hence an irreversible change has taken place. Proteins undergo irreversible changes and become insoluble in water by warming with dilute acids or dilute alkalis. This action is termed *denaturation*. The denatured proteins are soluble in dilute alkalis and acids.

When salts of heavy metals, *e.g.* copper sulphate or ferric chloride, or an acidified solution of mercuric chloride are added to a protein sol, the protein is precipitated as an insoluble compound. This also happens on the addition of gallic acid, trichloroacetic acid, sulphosalicylic acid, picric acid or phosphotungstic acid. The latter is used for the quantitative precipitation of proteins from solutions.

Proteins give various colour reactions.

1st The *biuret reaction*. A reddish violet colour is produced by adding a few drops of 2 % copper sulphate solution followed by dilute alkali to a protein sol. This is known as the biuret reaction because biuret (151) gives the same reaction; amino-groups and the amide group, (—CONH—), also occur in biuret.

2nd *Millon's reagent*. On boiling a solution of protein with mercuric nitrate containing nitrous acid, a red precipitate is produced if tyrosine is present as a structural unit in the protein.

3rd The *xanthoproteic reaction*. On treating albuminoid substances with nitric acid and then making alkaline, a yellow colour is produced if an amino-acid containing a benzene nucleus is present as a structural unit in the protein.

4th The *tryptophan reaction*. An equal volume of a solution of glyoxylic acid (CHOCOOH) is added to a protein sol and then strong sulphuric acid is carefully poured into the mixture to form a lower layer; a violet coloured ring is produced at the interface (HOPKINS-COLE). This reaction is given by proteins containing the tryptophan residue as a structural unit.

5th The *Pauly reaction*. On adding soda to a protein solution and then a solution of diazobenzenesulphonic acid, a red colour is produced which changes into a yellowish red on acidification. This reaction is given only by those proteins containing tyrosine or histidine as structural units.

201. Two large groups of proteins are distinguished.

1st *Proteins i.e. simple proteins*. On hydrolysis these compounds are converted almost exclusively into amino-acids.

2nd *Complex proteins, or conjugated proteins*, which are referred to in the older literature as *proteides*, a term now obsolete. On hydrolysis these substances give appreciable quantities of other products such as phosphoric acid, a saccharide, a nucleic acid or a colouring matter as well as amino-acids; thus they are made up of a protein and another component ("prosthetic group"; KOSSEL).

It is impossible to make a sharp distinction between the two groups because it is found that many proteins *e.g.* those from egg-white and those from serum, on hydrolysis afford small quantities of a mono-saccharide such as mannose or galactose.

To the first group belong the albumins, the globulins, the glutenins, the prolamins, the histones, the protamines and the scleroproteins.

Albumins are soluble in pure water, they are precipitated from neutral aqueous solutions only by high concentrations of neutral salts. They contain sulphur. Amongst the products of hydrolysis, glycine is present only in very small quantities. To this group of compounds belong the albumins

from serum, from white of egg, from milk (*lactalbumin*), *leucosin* from grain, *legumelin* from peas.

Globulins have weakly acid properties and are insoluble in pure water, soluble in dilute solutions of neutral salts, dilute acids or alkalis. They are precipitated from these solutions by adding ammonium sulphate (to about half the saturation concentration). Globulins occur in milk, white of egg, in different kinds of grain and in oil seeds; to this group belong also *fibrinogen* from blood, *myosin* from muscle and *edestin* from hemp-seed.

Glutenins are very similar in properties to the globulins but they are not soluble in dilute solutions of neutral salts. They occur in wheat, maize and rice.

Prolamins or *gliadins* differ from all others in that they are soluble in alcohol approximately 70 %. To this class belong *gliadin* from wheat, *zein* from maize, *hordein* from barley. On hydrolysis these substances produce *proline* and *glutamic acid* in appreciable quantities.

Histones are soluble in water and their solutions react alkaline. They are precipitated from aqueous solutions by adding ammonia or neutral salts. On hydrolysis appreciable quantities of diamino-acids (197) are produced. These structural units are responsible for the basic properties of the histones. Histones occur in the cell nuclei of animals; globin the protein in red blood cells also belongs to this group.

Protamines have basic properties and are soluble in water. The solutions are not coagulated on warming. On hydrolysis the protamines give mainly diamino-acids, the chief of which is arginine. To the protamines, which occur in fish roes, belong *clupeine* from herrings and *salmine* from salmon.

Scleroproteins occur in the animal organism in the insoluble state. To these belong *keratin*, a constituent of hair, wool, nails and hoofs; *collagen* a constituent of bones, cartilage and the connective tissue of skin and tendons, from which *gelatin* and *glue* are produced on heating with water; *elastin*, which occurs in the yellow, elastic connective tissue; *silk-fibroin* the constituent of silk fibres. To this class belong also *spongin*, a constituent of sponges and *gorgonin*, (199) a constituent of corals.

To the second group belong the phosphoproteins, the mucoproteins, the nucleoproteins and the chromoproteins.

Phosphoproteins give phosphoric acid on hydrolysis. They are insoluble in water but dissolve in alkalis, being reprecipitated from the alkaline solution by acids. To the phosphoproteins belong *casein*, the chief protein constituent of milk and *vitellin* from the yolk of eggs.

Mucoproteins are constituents of cartilage and mucoid substances from the animal organism. They contain a sulphate ester of a sugar derivative as prosthetic group. Glucosamine (171) or galactosamine is found amongst the

hydrolysis products (P. A. LEVENE). The mucoproteins to which the *mucins* belong, have acid properties.

Nucleoproteins consist of a protein combined with a nucleic acid (349). They are soluble in water, salt solutions and alkalis and have a faintly acid character. They occur in the nuclei of cells.

Virus bodies, which cause some of the infectious diseases, also belong to the nucleoproteins. The remarkable thing about these substances is that they can reproduce themselves in the living cell. The viruses have very high molecular weights (determined by the method of SVEDBERG). The virus which causes tobacco mosaic disease was the first to be obtained in a crystalline form (STANLEY); the molecular weight is of the order of 50×10^6 . The molecules of this virus can be rendered visible in the electron microscope and have the form of small rods with a length of about 300 m μ .

Chromoproteins. To this class of compounds belongs the red colouring matter of blood, *haemoglobin*, which consists of a compound of a protein, *globin* and a colouring matter containing iron, *haemochromogen* (319).

Haemoglobin combines very easily with atmospheric oxygen to form *oxyhaemoglobin*, which loses oxygen in a vacuum and is reconverted into haemoglobin. The significance of haemoglobin for respiration depends on this reversible reaction with oxygen. Carbon monoxide can combine with haemoglobin to form carbon monoxide—haemoglobin, which can then no longer take up oxygen; hence carbon monoxide is a poisonous substance. If air contains as little as 0.1 % of carbon monoxide, 50 % of the haemoglobin is converted into the compound with carbon monoxide.

The Structure of the Proteins

202. Some of the amino-acids, including glycine, leucine, and tyrosine were observed as fission products of proteins as early as the first half of the 19th century; in addition to amino-acids, some very different substances have been found in the chemical or fermentative degradation products of proteins, but only in small quantities; these include volatile fatty acids, benzene derivatives, skatole (315), ammonia and organic bases, but in the main amorphous ill-defined products are produced.

SCHÜTZENBERGER heated proteins under pressure with baryta water; barium salts of amino-acids were obtained which could not be separated by fractional crystallisation. Since the weight of decomposition products (after removal of the baryta) was more than that of the starting material, this increase must be attributed to combination with water. This indicates that a hydrolytic fission into amino-acids had taken place (1879).

E. FISCHER (1900) carried out the hydrolysis of proteins by boiling with hydrochloric acid or dilute sulphuric acid. The resultant amino-acids were converted into ester hydrochlorides by treatment with alcohol and hydrogen chloride; the free esters could be partially separated by fractional distillation at low pressure.

According to another method, the monoamino-acids were separated by extracting the aqueous solution of the hydrolysis products with butyl alcohol, in which the monoamino-acids dissolve preferentially, while the diamino-acids and amino-dicarboxylic acids remain in the aqueous layer (DAKIN).

Some amino-acids, like tyrosine and cysteine, which are sparingly soluble in water, can be isolated directly. The basic amino-acids like arginine, lysine and histidine, can be separated by precipitation with phosphotungstic acid; some of the ester hydrochlorides of the amino-acids, *e.g.* the hydrochloride of glycine ethyl ester, can be obtained from the hydrolysis product in a crystalline state.

The quantitative analysis of the mixture of amino-acids, produced by the hydrolysis of a protein, is very difficult. Special methods of determination are used for the different amino-acids.

Methods have also been worked out which depend on fractional adsorption on alumina, adsorptive carbon or certain synthetic resins. With the help of these methods it is sometimes possible to carry out the analysis on the hydrolysate from a small quantity of protein.

For the separation of closely related proteins such as occur for example, in serum, the method of TISELIUS, which depends on electrophoresis, is of great importance.

The percentage composition of the mixture of amino-acids produced on hydrolysis is given for a number of proteins in Table 37. The figures given are to be taken as average values.

It may be seen that the proportions of the amino-acid residues in the various proteins differ considerably. The glycine residue for example, is present in a high percentage in collagen but in a low percentage in casein. Alanine and leucine (or isoleucine) residues occur in most proteins, albeit in very different amounts.

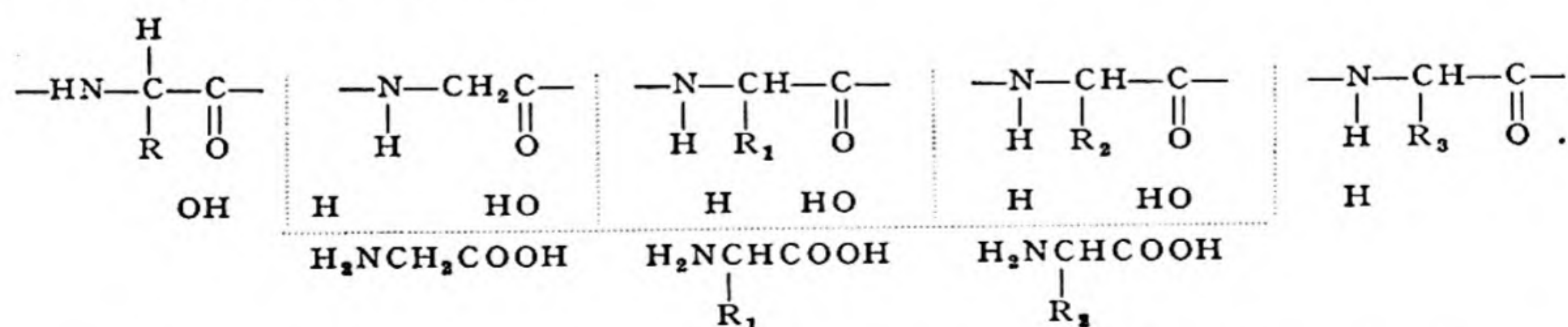
Albumin contains considerably more of the amino-acid residues containing sulphur (cystine and methionine) than collagen. The mixture of amino-acids from gliadin consists to the extent of about 50 % of glutamic acid. The hydroxyproline residue occurs in collagen but is missing in various other proteins. It may also be mentioned now that fibroin contains a high percentage of glycine and alanine residues and that a considerable percentage of cystine residues is present in keratin.

TABLE 37

PERCENTAGE COMPOSITION OF AMINO-ACIDS MIXTURE PRODUCED ON HYDROLYSIS OF SOME PROTEINS

Amino-acid	Proteins				
	albumin from hen egg	muscle tissue	collagen	casein	gliadin from wheat- gluten
Glycine	3.3	5.0	26.9	0.6	1.0
Alanine	7.4	4.0	10.5	2.8	2.5
Valine	6.8	5.8	2.4	6.7	3.0
Leucine	9.4	7.7	4.2	9.9	6.0
Isoleucine	5.6	6.3	1.9	6.5	
Serine	7.6	5.4	3.7	7.5	0.1
Threonine	—	4.6	1.7	4.1	3.0
Cystine	2.3	1.3	0.1	0.3	2.3
Methionine	5.0	3.3	1.1	3.5	2.3
Lysine	5.1	8.1	5.1	7.9	0.6
Arginine	5.8	7.7	10.3	4.2	3.2
Histidine	2.4	2.9	1.1	2.5	2.1
Aspartic acid	8.2	6.0	5.7	6.3	1.4
Glutamic acid	16.3	15.4	11.7	24.2	46.0
Phenylalanine	5.6	4.9	2.4	5.2	2.5
Tyrosine	4.4	3.4	0.3	6.9	3.1
Tryptophan	1.3	1.3	0.1	1.4	0.9
Proline	4.3	6.0	17.4	8.0	13.2
Hydroxyproline	—	—	14.8	0.0	—

On the analogy of the hydrolytic fission of amides, in which the bond between the carbon and nitrogen atoms in the group $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}_2$ is broken, various investigators (CURTIUS, E. FISCHER, HOFMEISTER) have assumed that the protein molecules are to be regarded as substituted amides according to the scheme:



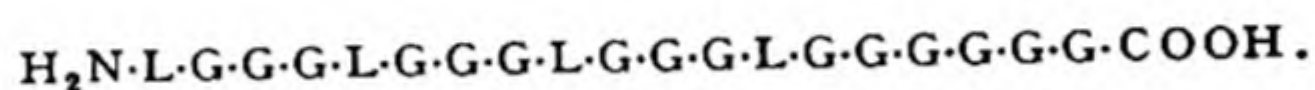
The bonds between the carbon and nitrogen atoms in the group $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\underset{\text{H}}{\underset{|}{\text{N}}}-$, i.e. the amide bonds, are broken on hydrolysis.

This opinion was converted into certainty, chiefly by the masterly researches of E. FISCHER and his co-workers. E. FISCHER prepared various *peptides* synthetically. These are compounds in which amino-acid residues are joined together as acid amides according to the above scheme. One speaks of di-, tri-, tetra- or polypeptides according to whether the molecule contains two, three, four or a large number of amino-acid residues.

It has also been found, that some of these polypeptides, in which the amino-acid residues have the same stereochemical configuration as the natural amino-acids, can be split up by proteolytic enzymes (see 207).

203. In the hydrolysis of proteins by the action of proteolytic enzymes, peptides, have been observed in some cases, as well as amino-acids; the former may therefore occur as intermediate products in this hydrolysis. Thus *glycylalanine* has been found in the enzymatic hydrolysis of fibroin.

The most complex polypeptide obtained synthetically contains nineteen amino-acid residues, fifteen of which are glycine residues and four leucine residues:



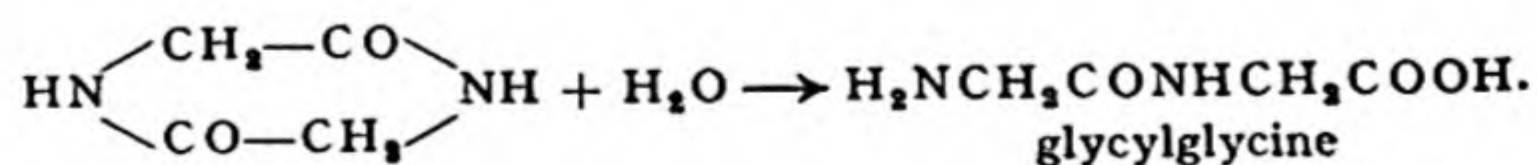
This polypeptide, $\text{C}_{54}\text{H}_{91}\text{N}_{19}\text{O}_{20}$, has a molecular weight of 1326, is amorphous and sparingly soluble in cold water. It is salted out from its solutions by saturating the liquid with ammonium sulphate. It is split up hydrolytically by ereptases (207). Other synthetic polypeptides of high molecular weight show a resemblance to the proteins in chemical and physical properties. Polypeptides, especially the lower ones, show the biuret reaction.

On the basis of the properties of synthetic polypeptides, it is assumed that peptide chains in which the amino-acid residues are joined together in an amide-like fashion also occur in the proteins.

From the above, the amino-acids are the final products of the hydrolysis of proteins. In the hydrolysis with acids or alkalis as well as with proteolytic enzymes, *proteoses* and *peptones*, substances which cannot be clearly defined and which are therefore to be regarded as mixtures of polypeptides, are produced as intermediate products.

A few of the various methods for the synthesis of peptides are given below.

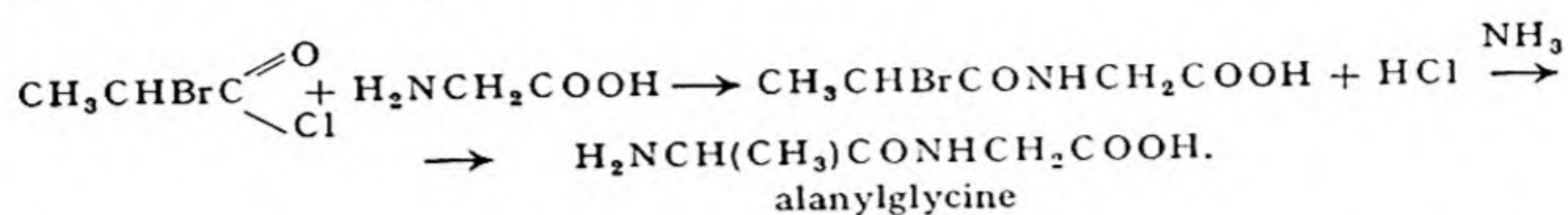
A di-peptide is produced by partial hydrolysis on warming a diketopiperazine (194, 341) with dilute alkali:



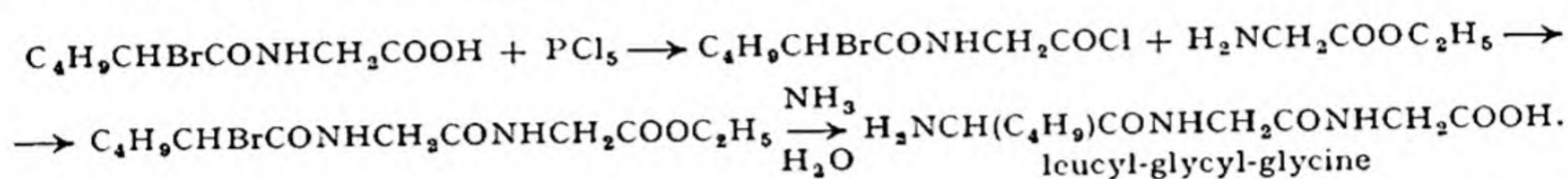
Alanylalanine, *leucylleucine*, etc. are prepared in a similar way.

By the action of the chloride of a halogeno-acid on an amino-acid in

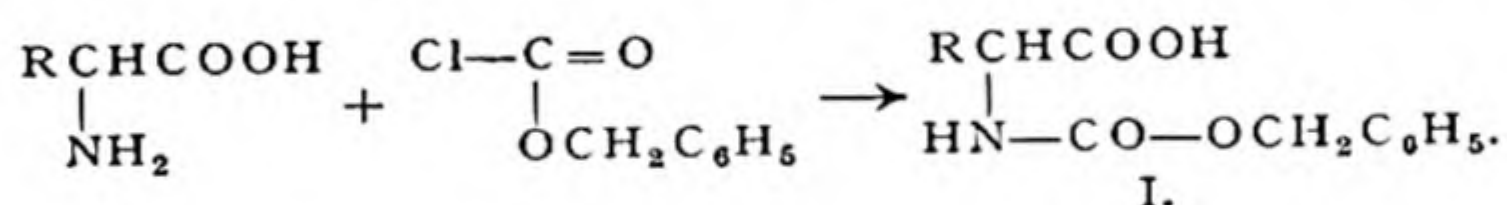
weakly alkaline media, an intermediate product is obtained, which can be converted into a dipeptide with ammonia:



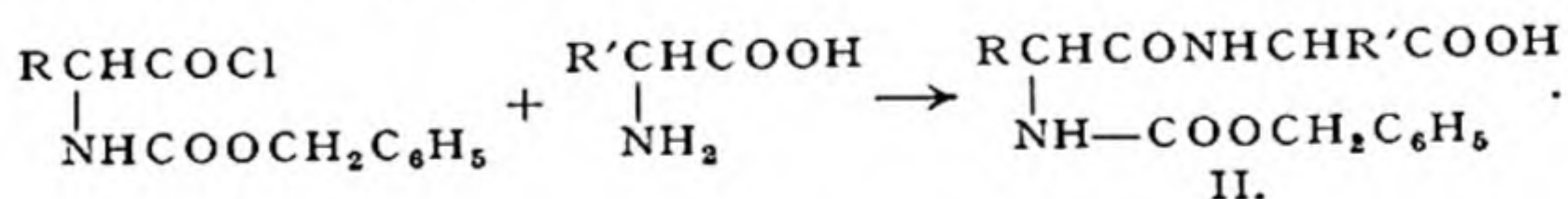
A third amino-acid residue may be introduced by taking, for example, a homologue of the intermediate product mentioned above, converting it into an acid chloride by the action of phosphorus pentachloride, and then allowing it to interact with an ester of an amino-acid, *e.g.* glycine. The resultant compound on hydrolysis and subsequent treatment with ammonia gives the tripeptide *leucyl-glycyl-glycine*:



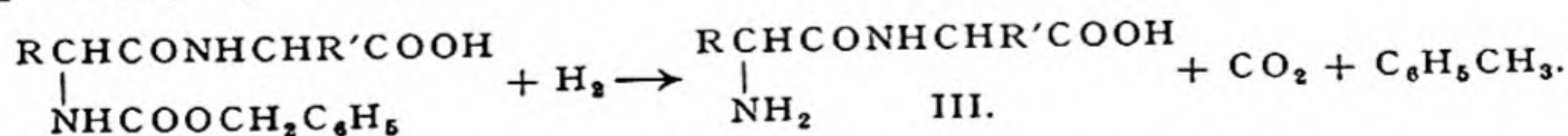
An improved method for the synthesis of peptides was discovered by BERGMANN and ZERVAS. By the action of benzyl chlorocarbonate on an amino-acid, a derivative (I) carrying a substituent on the amino-group, is produced and the amino-group is protected from further reactions:



(I) is then converted into an acid chloride, which is allowed to react with a second molecule of an amino-acid:



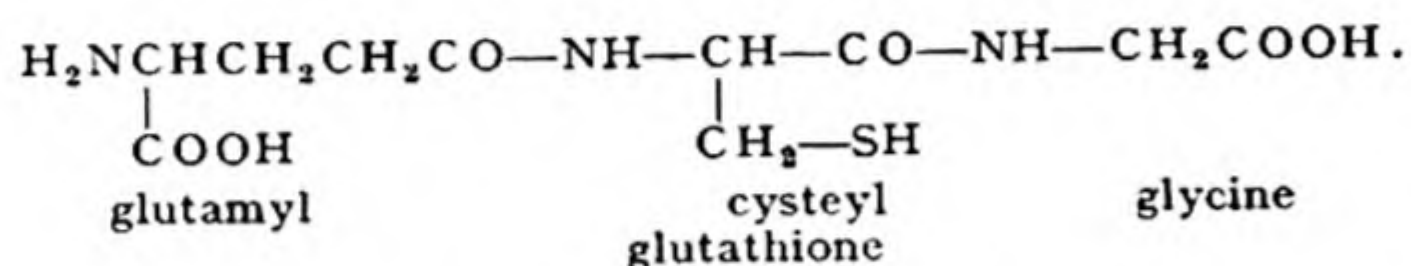
The $-\text{CO}-\text{OCH}_2\text{C}_6\text{H}_5$ group can be split off from compound II at ordinary temperatures by catalytic reduction with hydrogen and palladium, and a dipeptide, (III), is produced:



In this reaction hydrolytic fission of the dipeptide is not possible. Various dipeptides, which could not be prepared in any other way, have been made by this method; these include *glycylproline*, *lysylglutamic acid* and *lysylhistidine*.

In order to be able to compare these synthetic products with natural proteins, which are optically active, the syntheses have been carried out with optically active amino-acids. The latter are prepared by benzoylating (260) the inactive acids and resolving the racemic mixture of benzoyl compounds into the optically active components by conversion into alkaloid salts. The optically active acids are then obtained by splitting off the benzoyl groups. A large number of optically active peptides, including *l*-alanylglycine, *l*-alanyl-*l*-leucine, *l*-leucyl-glycyl-*l*-isoleucine, *l*-leucyl-glycyl-*l*-leucyl-glycyl-*l*-leucine, etc., have been prepared synthetically.

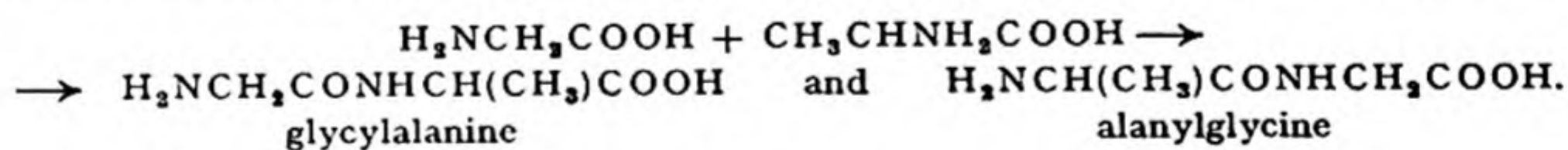
Glutathione, i.e. a glutamylcysteylglycine, as has been shown by its synthesis (HARINGTON), is an important tripeptide:



Glutathione occurs in yeast and in animal tissues (HOPKINS) and acts as an oxygen carrier; glutathione is readily oxidised to a disulphide (like cysteine to cystine) and the disulphide so produced is easily reconverted into glutathione by reduction.

The principle on which the proteins are built up is somewhat similar to the structure of the polysaccharides like starch and cellulose (181, 186). The difference is, however, that in the hydrolysis of polysaccharides only a few mono-saccharides (principally glucose) are produced but in the hydrolysis of proteins there is produced a large number of amino-acids; hence the structure of the protein molecule is much more complex than that of the polysaccharide molecule.

Two different amino-acids can give rise to two isomeric dipeptides, e.g.:



Three different amino-acids can form six isomeric tripeptides; the number of isomers rapidly increases with the number of different amino-acid residues. For twenty different amino-acid residues the number of isomers is given by the expression $20! = 20 \times 19 \times 18 \times \dots \times 1 \approx 2.3 \times 10^{18}$; stereoisomers are ignored in this calculation. On this hypothesis it is clear that the number of proteins which may occur in nature, is practically unlimited although the number of structural units from which these substances are constructed is limited relatively small.

204. Molecular weight of proteins. From experiments on the dialysis of proteins it was realised that the molecules of these substances are very large.

Determination of the molecular weight by measuring the osmotic pressure is fraught with great experimental difficulties and has led to reliable results in a few cases only.

Another method by which the molecular weight of proteins and other soluble colloids can be determined but depending on quite a different principle, has been discovered by THE SVEDBERG. The vessel containing the protein sol is placed in an *ultracentrifuge*, which can be rotated at 150,000 revolutions per minute. By this means the solution is subjected to a very high centrifugal force as a result of which the protein molecules orientate themselves in the direction of the force. This orientation is opposed by the forces exerted on the protein molecules as a result of BROWNIAN movement, so that eventually a condition of equilibrium, the *sedimentation equilibrium*, is set up. The change in the concentration in the direction of the centrifugal force can be measured during the centrifugation, with the aid of optical methods *e.g.* by determining the absorptive power for ultra-violet light or the refractive index of the solution. The weight of the protein particles can be calculated from the concentration prevailing at the sedimentation equilibrium.

A great advantage of the SVEDBERG method is that it gives an answer to the question whether a protein sol is *homodispersed*, *i.e.* contains exclusively particles of the same size, or *heterodispersed*, *i.e.* particles of different sizes. It is even possible to determine the weights of different sized particles occurring alongside one another in a solution.

From these investigations it has been found that natural proteins are either *homodispersed* or *paucidispersed*, *i.e.* consist of only few molecular species; *polydispersity* occurs only in artificially modified proteins. It is a remarkable fact that the molecular weights of a number of proteins can be represented approximately by the number 17600 or a multiple of it (Table 38).

TABLE 38

MOLECULAR WEIGHTS OF SOME PROTEINS ACCORDING TO SVEDBERG

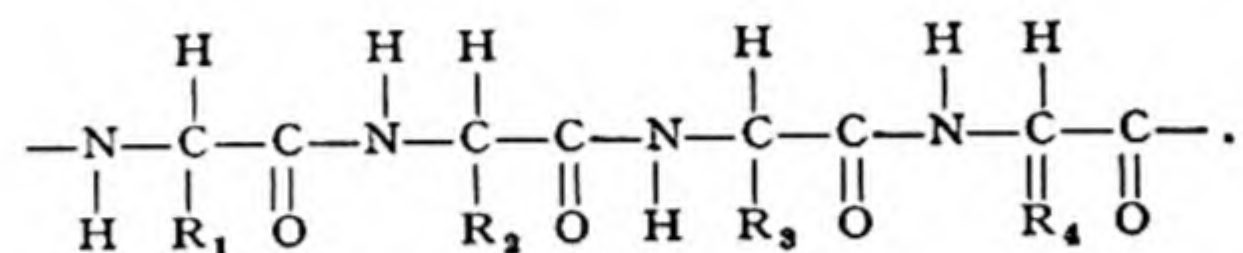
Protein	Molecular weight	
Albumin from milk	17,500	
Albumin from eggs	40,500	} $2 \times 17,600 = 35,200$
Globulin from milk	37,900	
Pepsinase	39,200	
Insulin	35,100	
Haemoglobin	63,000	} $4 \times 17,600 = 70,400$
Albumin from serum (horse)	66,900	
Globulin from serum (horse)	150,000	$8 \times 17,600 = 140,800$
Haemocyanin (<i>homarus</i>)	803,000	$46 \times 17,600 = 809,600$
Haemocyanin (<i>helix pomatia</i>)	6,680,000	

The molecular weights of a few proteins have been determined also by osmotic methods and found to agree with those determined by the SVEDBERG method.

It is noteworthy that very high molecular weights have been found for the chromoproteins from the blood of some invertebrates.

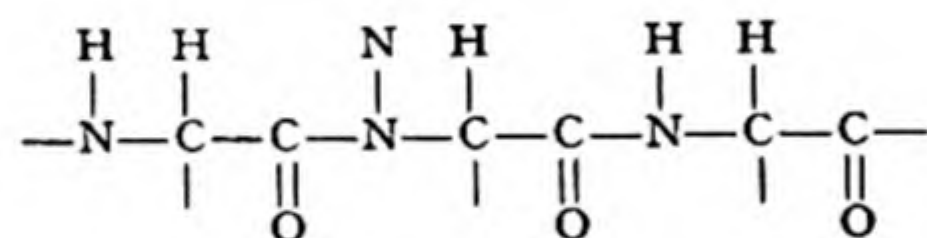
The protamines have much lower molecular weights than other proteins; *salmine*, for example, has a relatively simple structure. It contains 40 arginine, 7 serine, 4 proline, 3 glycine, 2 valine, 1 isoleucine and 1 alanine residues. This corresponds to a molecular weight of about 8000.

As already pointed out, the polypeptide chains in proteins have the structure:



In glycine, residue R is a hydrogen atom, in the other amino-acids, R is a hydrocarbon radical, which may or may not be substituted by other groups (OH, SH, COOH, NH₂ or cyclic nuclei).

These R groups form the side-chains, the main chain is formed by the grouping:



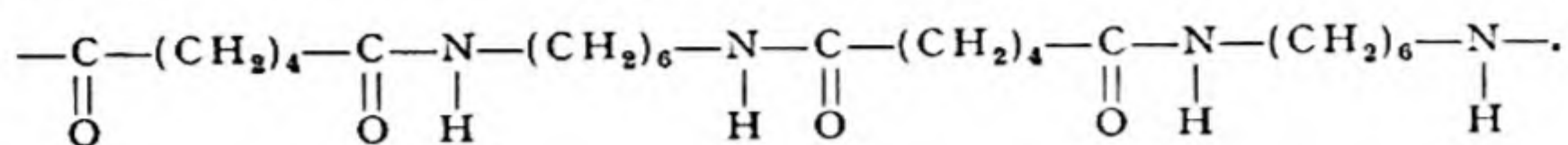
repeated time after time.

From the X-ray examination of fibroin, which is built up mainly of glycine, alanine and tyrosine residues, it is found that the principal chains are orientated roughly parallel with the long axis of the fibroin fibre. The same holds for keratin in the stretched state. Hence the fibres of fibroin or of stretched keratin consist of parallel bundles of thread-like molecules (ASTBURY).

Proteins like haemoglobin and edestin also show a crystalline but not a fibre-like structure. From measurements made by SVEDBERG it is probable that the micelles of these and various other soluble proteins in solution are roughly spherical in shape; besides the polypeptide chains, these micelles also contain water molecules, which are present as "water of crystallisation" in undried albumin crystals. These proteins show a fibre diagram in the denatured state.

The acid amide bond of the polypeptide chains also occurs in synthetic substances of high molecular weight known as polyamides. In the manufacture of these substances a mixture of an $\omega\omega'$ -dicarboxylic acid and an $\omega\omega'$ -diamine, e.g. 1,6-diaminohexane and butane 1,4-dicarboxylic acid, is heated. A reaction takes place by which an atom

of hydrogen from the amino-group reacts with a hydroxyl group in a molecule of acid, with the formation of a molecule of water. As the result of this *polycondensation reaction* linear macro-molecules are produced (CAROTHERS):

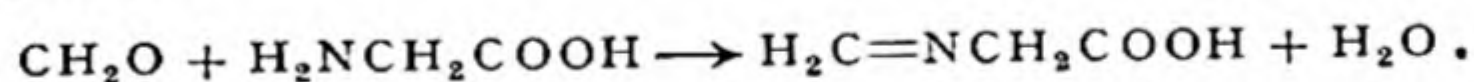


In this way a plastic material is obtained, which can be drawn out to give fine threads (*Nylon*).

205. Enzymatic degradation of proteins. Some account will be given on the general properties of enzymes and their reactions in the next chapter, but the main points connected with the enzymatic degradation of proteins and polypeptides will be discussed here. The proteolytic or protein-splitting enzymes are designated by the collective name *proteases*. Examination of the action of the various proteases proved very difficult because initially investigators always worked with mixtures of different enzymes. More insight into the specific action of the various enzymes was obtained when it was discovered how to separate one species of enzyme only from these mixtures containing several.

In the enzymatic fission of proteins the amide bonds, $\begin{array}{c} \text{—C—N—} \\ || \quad | \\ \text{O} \quad \text{H} \end{array}$, known also in this case as *peptide bonds*, are split hydrolytically; it has been shown, that in the partial hydrolysis of proteins into smaller molecules (polypeptides), COOH groups and NH₂ groups are always produced in equivalent quantities as is to be expected if the protein molecule consists of a polypeptide chain.

The free carboxyl groups in peptides or amino-acids can be determined by the method of SÖRENSEN. A solution of formaldehyde is first added, which reacts with the free amino-groups:



The derivatives so obtained no longer possess any basic properties, so that the number of carboxyl groups can be determined by titration.

Free amino-groups in proteins or peptides can be determined by the VAN SLIKE method, in which the volume of gaseous nitrogen produced after the addition of nitrous acid, is measured.

The proteases are divided into two main groups: the *proteinases* and the *peptidases*; both groups comprise various sub-groups. Proteinases split proteins into smaller molecules (polypeptides) and can also split up synthetic polypeptides in which at least two successive peptide bonds occur. Proteinases are unable to break down proteins completely to amino-acids; for this purpose it is necessary to use peptidases as well.

Peptidases are divided into:

carboxypeptidases, which split off the terminal amino-acid carrying the COOH-group from a polypeptide;

aminopeptidases, which split off the terminal amino-acid carrying the NH₂-group;

dipeptidases, which only split dipeptides.

The fact that natural proteins are not attacked by peptidases is in accordance with this division; on account of the high molecular weight of the proteins the system contains only very few free amino-groups and free carboxyl groups, so that the initial breakdown can only be brought about by means of the proteinases, which do not cause attack on the terminal groups but split peptide bonds in the chain.

For investigations on the specific action of the three groups of peptidases mentioned above, use has been made of synthetic polypeptides of simple structure, so that the amino-acids produced on fission can be easily identified. It should be mentioned that optically active amino-acids of the *l*-series were used for the synthesis of these polypeptides.

The following are examples of proteinases ¹⁾:

1st *pepsinase*, which is most active in an acid medium ($p_H = 2$). There is present in the mucous membrane of the stomach a substance called *pepsinogen*, from which *pepsinase* is produced by the influence of pepsinase already present in the gastric juice, *i.e.* by an autocatalytic process.

2nd the *papainases*, which are active in weakly acid or neutral media ($p_H = 4$ to 7); they occur in vegetable and animal cells (*e.g.* in the milky juice from the melon tree, *Carica papaya* L.).

3rd the *trypsinases* which are active in an alkaline medium ($p_H = 8$ to 9); these occur in the pancreas and in the intestines; trypsinase is produced in the small intestine from *trypsinogen*, a substance formed in the pancreas; the conversion of trypsinogen into trypsinase can be brought about both by trypsinase itself (autocatalytically) or by *enterokinase*, another enzyme present in the mucous membrane of the intestine.

4th *chymotrypsinase* which occurs in the pancreas and is active at $p_H = 8$ to 9 .

Carboxypeptidases, aminopeptidases, and dipeptidases also occur in the mucous membrane of the small intestine and in the pancreas as well as trypsinases.

A number of proteases including dipeptidases, aminopeptidases and papainases, occur also in yeast.

¹⁾ In many English books and journals the ending "ase" is frequently deleted from the names of some, but not all, of the proteases, the older unsystematic name still being used, thus, *e.g.* pepsinase is called *pepsin*, papainase *papain*, trypsinase *trypsin*, etc., but enterokinase is always so called and is never abbreviated to enterokin.

From the above it is apparent that there is a great difference between the hydrolysis of proteins by dilute acids and by proteases. All the peptide bonds are split hydrolytically by dilute acids. On the other hand, a definite enzyme acts on particular peptide bonds and leaves others unattacked.

206. Biochemical synthesis of proteins from amino-acids. The amino-acids formed in the digestive tract by degradation of the proteins present in food, are partially reused for the synthesis of those special proteins, which the living organism requires for its maintenance or its growth. It is postulated that this synthesis of proteins from amino-acids depends in the action of enzymes. ROSE concludes from his elaborate investigations that the amino-acids listed in the left-hand column of Table 39 are essential for the human organism (1947).

TABLE 39
ESSENTIAL AND NON-ESSENTIAL AMINO-ACIDS ACCORDING TO ROSE

Essential amino-acids	Non-essential amino-acids, which can be left out
Valine	Glycine
Leucine	Alanine
Isoleucine	Arginine
Lysine	Serine
Methionine	Aspartic acid
Threonine	Glutamic acid
Phenylalanine	Proline
Tryptophan	Hydroxyproline
	Histidine
	Tyrosine
	Cystine

Of the 19 amino-acids met with as structural units in proteins occurring in foodstuffs, 8 are essential; it must be supposed that these essential amino-acids cannot be synthesised by the human organism, while the other 11 amino-acids can.

As regards the effect of stereochemical configuration, it has been found that *d*-methionine is as effective for growth as *l*-methionine, the same holds for tryptophan, histidine and phenylalanine the *l*-forms of which can be replaced by the *d*-form. On the other hand, only the *l*-forms of valine, leucine, isoleucine and lysine and the *d*-form of threonine can be used by the animal organism.

(xiv) ENZYMES AND ENZYMATIC REACTIONS

207. Enzymatic reactions have been brought to notice several times already in this text-book: by *enzymes* (εν ζυμη = in yeast) or *ferments* (abbreviation of fervimentum, fervere = to boil, ferment) are meant substances produced by vegetable or animal organisms and which can bring about various chemical reactions like hydrolytic fissions, oxidations and reductions and sometimes even the fission of carbon chains, by catalytic action. The enzymes are *biocatalysts*, which initiate and regulate chemical reactions in the living organism. They are denoted by the suffix *ase* and are divided into groups according to their mode of action; the chief groups are:

1st the *esterases*, which split *i.e.* hydrolyse, esters, and to which belongs, for example, chlorophyllase (321). The most important of the esterases belong to the sub-group of the *lipases* (114), which split fats (λιπος = fat) and which can also split other esters of mono- and polyhydric alcohols.

2nd the *carbohydrases*, which split di- and poly-saccharides; to this class belong, for example, *maltase* which splits maltose and *invertase*, which splits sucrose (176); the starch splitting enzymes, the *amylases*, which occur in saliva (*ptyalase*), in the pancreas and in vegetable organs, *e.g.* in germinating barley. The amylases occurring in the above are sometimes collectively called *diastases*.

3rd the *proteases*, which split proteins and polypeptides (200, 203).

4th the *oxidases*, which bring about oxidations, *e.g.* of phenols and amines, like histamine (199) and adrenaline (239, 307) by the transference of oxygen. To this group also belong the respiratory enzymes (351).

5th the *dehydrogenases* which bring about reductions by the transference of hydrogen (see 351).

6th the *zymases* which cause alcoholic fermentation (192).

In so far as they have been investigated, the enzymes have high molecular weights and show the typical properties of colloids. The enzymes sometimes occur in the form of colloidal solutions in body fluids such as saliva, blood, gastric juice and pancreatic fluid or they are found inside the cells. In the latter case, the enzymes are combined with the protoplasm and cannot be separated from it.

Since enzymes occur in living organs alongside other substances which show no enzymatic action, and they are difficult to purify on account of their colloidal properties, the isolation of enzymes in a pure state is a difficult task. The first important results in this field were obtained by WILLSTÄTTER and his collaborators (1920–1934). He made use of aluminium hydroxide and clay earths on which the enzymes present in vegetable or animal extracts were adsorbed. By a suitable choice of absorbent it is

possible to bring about selective adsorption and so free the enzyme, at least partially from admixed products. By washing the absorbent with a suitable solvent, *e.g.* a basic phosphate solution, the enzyme is again brought into solution and the purification by fractional absorption repeated. In order to have a measure of the concentration of an enzyme in a particular preparation, WILSTÄTTER determined the velocity of a reaction brought about by a definite amount of the enzyme preparation, *e.g.* the hydrolysis of cane-sugar or of a fat under accurately controlled conditions; in this way it was possible to check the methods of extraction and the degree of purification. For example, an invertase preparation was obtained in which the concentration of enzyme was about 2000 times greater than that in yeast and a lipase preparation in which the concentration of the enzyme was about 300 times greater than that in the pancreas. Notwithstanding this great step forward it is still uncertain whether the specimens obtained by WILSTÄTTER consist of pure enzymes. Nothing is yet known of the chemical structure of invertase or of the other carbohydrases or of the numerous esterases.

208. *Urease*, the enzyme which brings about the hydrolytic fission of urea into carbon dioxide and ammonia (151) and which occurs for example, in soya-beans, was the first enzyme to be obtained in a crystalline state (SUMNER 1926). Urease is a protein and belongs to the globulin group; its molecular weight by SVEDBERG's method is about 480,000. A few years later NORTHROP and his co-workers obtained various enzymes from the digestive tract in a crystalline state by adding ammonium sulphate and magnesium sulphate to extracts of the organs and repeating this method of precipitation. In this way crystalline preparations of pepsinogen and pepsinase, chymotrypsinogen and chymotrypsinase, trypsinogen and trypsinase, were obtained. These enzymes are all proteins and the crystals resemble other protein crystals. The molecular weight of pepsinase is 35,000 (determined by both the osmotic method and that of SVEDBERG), while that of trypsinase is 34,000. It is not yet known whether or not the action of these enzymes is connected with definite groups of atoms in the molecule.

WILSTÄTTER is of the opinion that, in general, enzymes consist of two constituents: a specific constituent (*agon*), which is responsible for the enzymatic action and which is combined with a colloidal constituent, which acts as a carrier (*pheron*). The combination of carrier and specific component should be necessary for the powerful and specific catalytic effect shown by the enzyme; an analogy for this is found in active inorganic hydrogenation catalysts, where finely divided platinum or nickel (the catalytically active substances) are deposited on a colloidal carrier such as aluminium hydroxide or carbon.

This opinion of WILLSTÄTTER appears to be correct for the yellow respiratory ferment of WARBURG (351) and for the hydrogen transferring ferments (351). In these enzymes the structure of the specific component, which is attached to a protein, is known. The specific component is called a *co-enzyme* (*co-ferment*), the protein attached to it is called the *apo-enzyme* (*apo-ferment*) and the whole combination of the two is called a *holo-enzyme* (*holo-ferment*). In some cases the co-enzyme has been separated in a pure state from the holo-enzyme, e.g. co-zymase the structure of which is known (351). In this case a dissociation-equilibrium exists: $\text{holo-enzyme} \rightleftharpoons \text{apo-enzyme} + \text{co-enzyme}$.

From the foregoing it is clear, that only in a few cases any insight into the chemical structure of enzymes has been obtained. Some general remarks may be made, however, on the action of enzymes.

Enzymes are very active catalysts, which bring about certain reactions even in very small quantities. This action is limited to narrow temperature limits, enzymes are only very slightly active at 0° and are decomposed at a temperature of 100° . For the majority of enzymes there exists an optimum temperature at which they are most reactive. This is in the neighbourhood of 37° for enzymes occurring in warm blooded animals and round about 15° for vegetable enzymes.

Enzymatic action is frequently strongly influenced also by the hydrogen-ion concentration of the medium and the concentration of the substance being decomposed by the particular enzyme. Further, enzymatic action can be affected by small quantities of certain substances, which are able to increase or decrease the activity or even to inhibit it altogether. An example of the latter effect is that of hydrogen cyanide on oxidases.

The *specific action of enzymes* is highly characteristic of enzymatic reactions. This means that a particular enzyme acts only on one particular substance or very closely chemically related substances. All disaccharides are hydrolysed by the action of dilute acids but *invertase* from yeast brings about exclusively the hydrolysis of sucrose and not that of maltose. Types of yeast are also known, e.g. *schizosaccharomyces octosporus* (BEYERINCK), which cause the fermentation of maltose but not of sucrose. It is assumed that this type of yeast contains no invertase but contains maltase, the enzyme which splits maltose.

The specificity of enzyme action is clearly brought out in the fermentation of monosaccharides. Of the monosaccharides containing from three to ten atoms of oxygen inclusively, only trioses, hexoses and nonoses can be fermented. These are also the only monosaccharides which from their composition can be broken down quantitatively into carbon dioxide and ethyl alcohol.

d-Glucose, *d*-mannose and *d*-fructose can be fermented very rapidly; the

mirror image forms of these sugars, *l*-glucose, *l*-mannose and *l*-fructose, which do not occur in nature, are either unattacked or attacked very much more slowly by brewers' yeast (E. FISCHER).

The fission of α -glucosides by maltase (168) and that of β -glucosides by emulsinase, an enzyme from bitter almonds, (179), have already been discussed in previous paragraphs.

Thus it follows from these examples, that the action of an enzyme is closely connected with the stereochemical structure of the substances on which the enzyme acts. Examples of specific action by proteases in the fission of proteins, have already been given in 205.

The vitamins and the hormones, which will be discussed in 306, are similar to enzymes in their action.

(xv) ASYMMETRIC SYNTHESIS

209. In the synthesis of compounds containing one asymmetric carbon atom, a mixture of equal amounts of optical antipodes or a racemic compound is always formed, so that optically inactive substances are obtained starting from inactive material. In the vegetable kingdom sugars, proteins and many other substances are produced in optically active forms, although the starting material, from which the plant builds up these substances, namely, water, carbon dioxide, nitrates and ammonia, is optically inactive.

Hence the question arises how is it possible for syntheses in living nature to proceed asymmetrically, *i.e.* to give rise to optically active end-products? First of all we will consider so-called *partial asymmetric syntheses*, in which the starting material is a substance, which already contains an asymmetric carbon atom and in which a second asymmetric carbon atom is introduced. By the addition of hydrogen cyanide to arabinose (161, 165) and hydrolysis of the hydroxycarbonitrile which is formed, there is produced a mixture of mannonic acid and gluconic acid in unequal amounts. These substances are stereo-isomers but not optical antipodes, so that the chance of formation for the two substances is not the same and one can therefore be produced in larger amounts than the other.

When benzoylformic acid is reduced, *dl*-mandelic acid (265) is produced. When the *l*-menthyl ester (obtained from *l*-menthol and benzoylformic acid) is reduced however, a mixture is produced consisting of the ester of *d*-mandelic acid with a slight excess of the ester of *l*-mandelic acid, from which a mixture of *d*- and *l*-mandelic acid is obtained by hydrolysis (*i.e.* by removal of the asymmetric grouping which had been introduced), in which the *l*-acid is present in slight excess. In a similar way a slight excess of *l*-lactic acid is obtained from the *l*-bornyl ester of pyruvic acid. In these examples the synthesis proceeds asymmetrically because one of the starting products already has an asymmetric structure.

A synthesis can also proceed asymmetrically under the influence of an optically active catalyst. The addition of hydrogen cyanide to benzaldehyde in chloroform as the solvent, under the catalytic influence of laevo-rotatory quinine or dextro-rotatory quinidine, on hydrolysis of the nitrile affords dextrorotatory mandelic acid in the first case and laevo-rotatory mandelic acid in the second case. From this it follows that under the influence of quinine the dextro-rotatory nitrile is formed more rapidly than

the laevo-rotatory and under the influence of quinidine the formation of the laevo-rotatory nitrile proceeds more rapidly than the formation of the dextro-rotatory component (BREDIG). Other examples of the specific action of optically active catalysts have already been given in sections 92 and 138.

Since synthesis in living cells takes place under the influence of optically active enzymes or of optically active constituents of the protoplasm, it can be particularly favoured in one direction, so that eventually, *d*-glucose is produced in the assimilation process for example. The fact that optical antipodes can behave differently in biochemical reactions (see 138, 205) is strictly analogous.

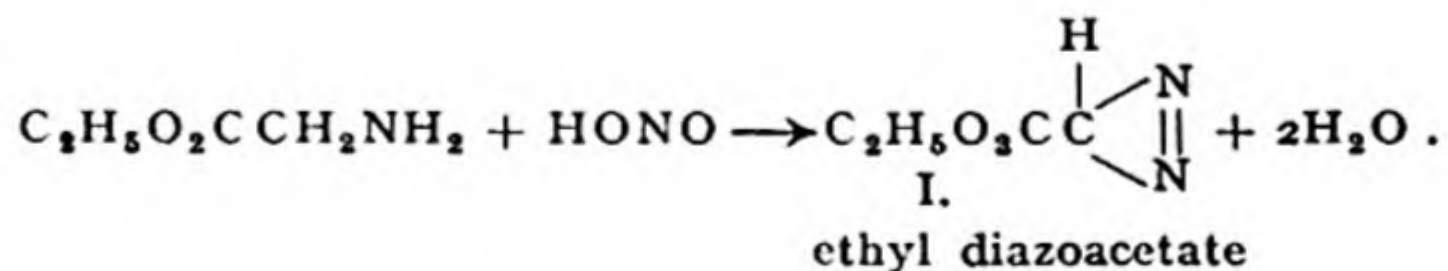
The question as to how the first optically active substance was produced in nature, cannot yet be answered. In this connection interesting experiments have been undertaken on the photochemical decomposition of racemic mixtures.

Circularly polarised light can be absorbed in varying degrees by a solution of an optically active substance, according to whether the light which passes through the solution is circularly polarised in a right or left hand direction. COTTON discovered this phenomenon, which is called *circular dichroism*, in 1896 in solutions of alkali copper *d*-tartrate. If an optically active substance can be decomposed by light and if the wave-length of the light causing this decomposition is about the same as the wave-length at which the *Cotton effect* occurs, then the possibility arises of the production of optical activity as a result of a photochemical reaction. When a mixture of equal quantities of optical antipodes is irradiated with right-handed circularly polarised light, for example, one antipode will be decomposed more rapidly than the other, so that the liquid will become optically active. Some examples of this are known (S. MITCHELL; W. KUHN).

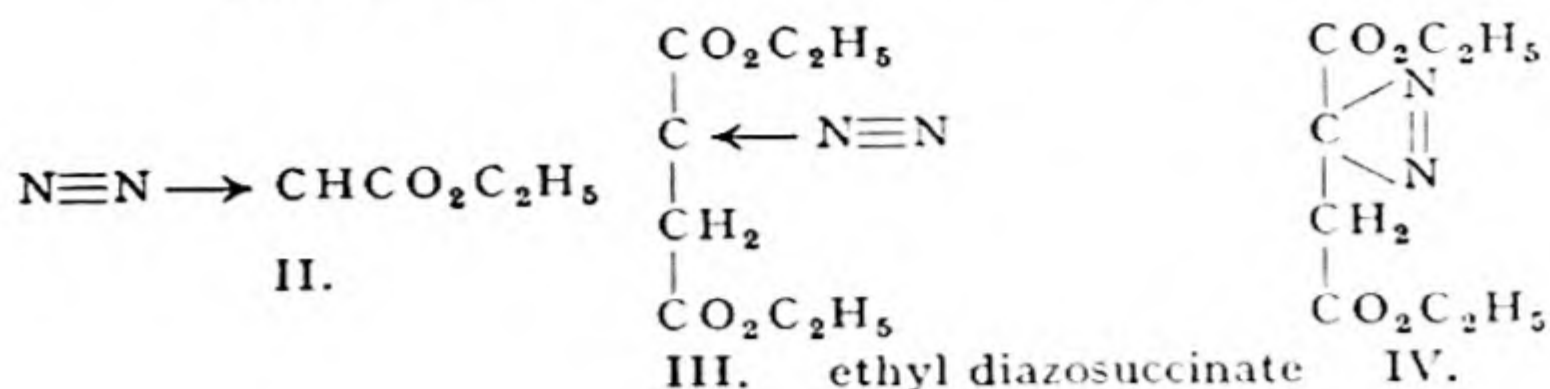
It may be assumed that optically active substances are produced in nature by photochemical decomposition of a racemic mixture, since a small excess of elliptically polarised light of a particular direction of rotation can be present in sunlight.

(xvi) ALIPHATIC DIAZO-COMPOUNDS

210. A compound belonging to this group was first obtained by CURTIUS (1883) by the action of nitrous acid on the ethyl ester of glycine; a yellow liquid having the composition $C_4H_6O_2N_2$, *diazoacetic ester* (ethyl diazoacetate) was produced and to it was ascribed the structural formula (I) given below:



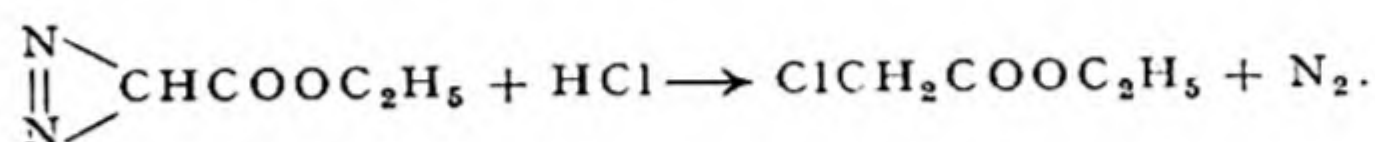
Besides the cyclic structure I, structure II, with a semipolar double bond, also comes into consideration for ethyl diazoacetate. An optically active diazosuccinic ester III can be obtained from ethyl *l*-aspartate (LEVENE and MIKESKA). This is in agreement with a semipolar structure for the group $N_2C<$ but not with the cyclic structure IV, since, in the latter case, the molecule would contain no asymmetric centre:



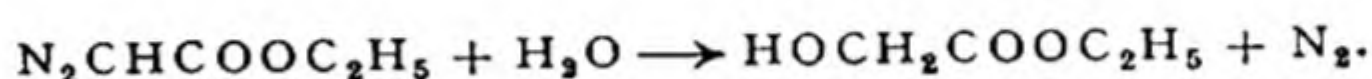
The reactions of ethyl diazoacetate are compatible with both formula I and formula II.

Diazoacetic esters are able to undergo a number of reactions, in which the two atoms of nitrogen are replaced by two mono-valent groups or atoms.

1. With concentrated hydrochloric acid, nitrogen is evolved and an ester of monochloroacetic acid is produced:

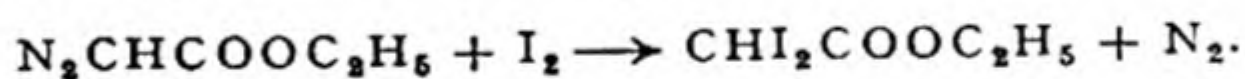


2. Esters of glycollic acid are produced with dilute acids, nitrogen being evolved:

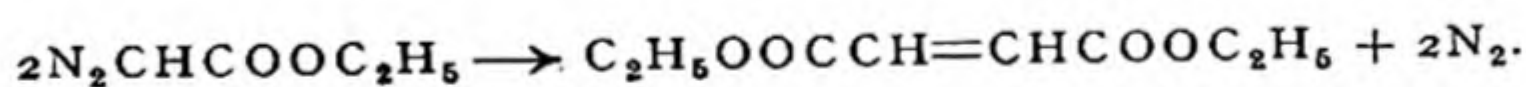


This reaction is a reaction of the first order, the velocity constant being directly proportional to the concentration of hydrogen ions, which act catalytically. Hence the determination of the velocity of this reaction (measurement of the amount of nitrogen evolved in a certain time) is a means of determining hydrogen ion concentration (BREDIG).

3. An ester of diiodoacetic acid is produced by the action of iodine:



4. On heating a solution of an ester of diazoacetic acid in ligroin in presence of a copper powder catalyst, the corresponding ester of fumaric acid is produced:

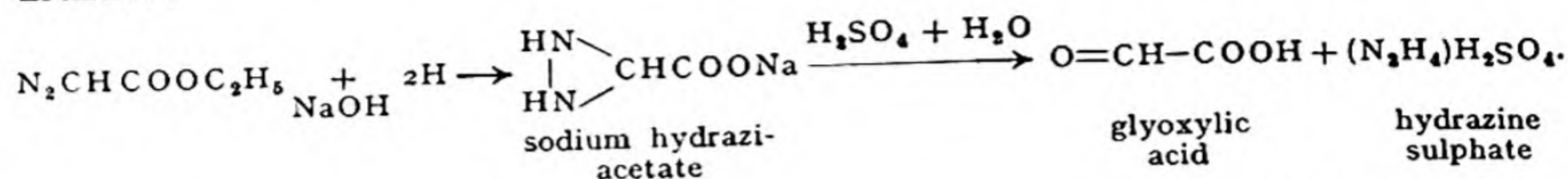


The reactions mentioned above are in accordance with the suggested structural formula. Ethyl diazoacetate is a comparatively unstable substance which undergoes slow decomposition at ordinary temperatures. On heating this decomposition takes place explosively.

A second group of reactions, which esters of diazoacetic acid can undergo, are those in which the diazo-group, $-\text{N}=\text{N}-$, breaks one of its bonds with the neighbouring carbon atom. In this case *pyrazole derivatives* (see 323) are produced.

A third group of reactions comprise additions, in which the double bond between the nitrogen atoms is converted into a single bond. By addition of hydrogen (by the action of zinc dust in alkaline solution) and simultaneous

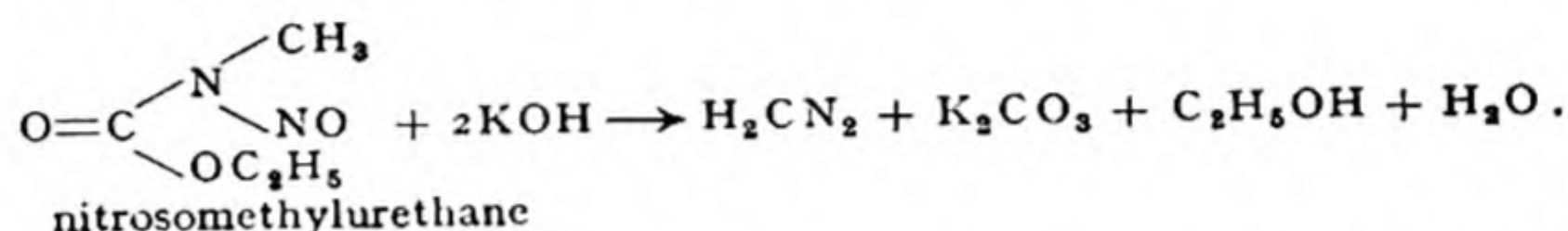
hydrolysis there is produced a salt of *hydraziacetic acid*, which is decomposed by acids at ordinary temperatures into glyoxylic acid and a salt of hydrazine:



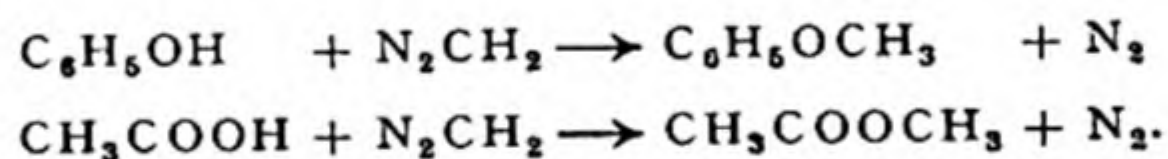
Hydrazine was discovered by CURTIUS by means of this reaction.

The hydrogen atom in the N_2CH -group in alkyl diazoacetates is replacable by metal. Sodium, for example, dissolves in the ester with the evolution of hydrogen.

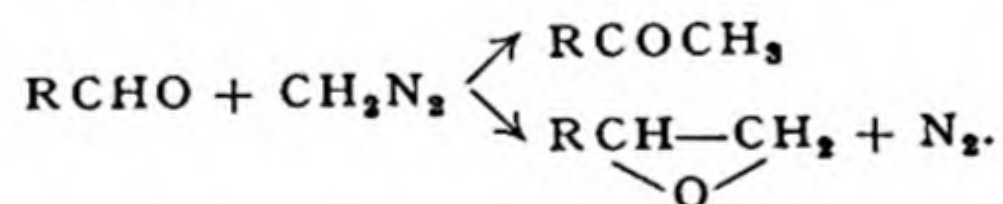
The simplest diazo-compound is *diazomethane*, $\begin{array}{c} \text{N} \diagup \\ || \\ \text{N} \diagdown \end{array} \text{CH}_2$, which may be prepared by the action of alcoholic potash on an ethereal solution of nitrosomethylurethane:



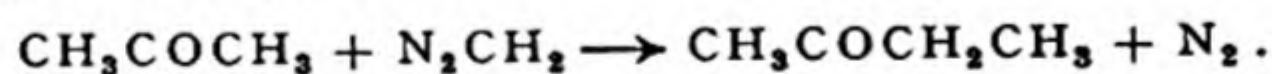
Diazomethane is a yellow coloured gaseous substance, readily soluble in ether; it is very poisonous. It is an unstable compound rapidly decomposing even in ethereal solution. An ethereal solution of diazomethane is used as a methylating agent, since this substance reacts with both carboxylic acids and with phenols with the evolution of nitrogen according to the equations:



Aldehydes react with diazomethane in two ways with the formation of ketones and the isomeric ethene-oxides:



Diazomethane reacts with ketones on the addition of water or methyl alcohol, which act as catalysts, as follows:



PART TWO
CARBOCYCLIC COMPOUNDS

CARBOCYCLIC COMPOUNDS

211. Those compounds are included in the cyclic compounds, which contain in their molecules a closed chain of atoms which remains intact during chemical reactions. Compounds with molecules containing a closed chain of atoms, such as anhydrides and imides of dicarboxylic acids, lactones and monosaccharides, have already been discussed in part one of this book; on hydrolysis, however, these compounds are easily converted into open chain compounds, so that a great difference exists between these groups of compounds and cyclic compounds proper. Cyclic compounds are divided up as follows:

A. *Carbocyclic compounds* in which the closed chain of atoms consists exclusively of carbon atoms. These are sub-divided into:

1. *Aromatic compounds or benzene derivatives*. Compounds with *condensed rings*, i.e. with two or more closed chains of atoms having at least two atoms in common, like naphthalene $C_{10}H_8$, which contains two six-rings, anthracene $C_{14}H_{10}$, which contains three six-rings, etc., are also included in this class.

2. *Alicyclic compounds*. These are the *cyclanes* and their derivatives to which the important group of terpenes belongs.

B. *Heterocyclic compounds*. The closed chain of atoms in this class consists of one or more atoms of other elements besides carbon atoms. Examples of these are *pyridine*, C_5H_5N and its derivatives in which a ring of five carbon atoms and a nitrogen atom occurs, *pyrone derivatives* with a ring of five carbon atoms and one oxygen atom, *furan* C_4H_4O with a ring of four carbon atoms and one oxygen atom, *pyrrole* C_4H_5N with a ring of four carbon atoms and one nitrogen atom, *thiophen* C_4H_4S with a ring of four carbon atoms and one sulphur atom, *pyrazole* $C_3H_4N_2$ with a ring of three carbon atoms and two nitrogen atoms and many others. To this class belong also compounds in which dissimilar rings occur having at least two atoms in common, like *quinoline* C_9H_7N , which contains a benzene ring and a pyridine ring in the same molecule.

About 4,000 ring systems are known; since numerous derivatives of each of these basic types are known, the number of cyclic compounds is very large indeed.

CHAPTER 9

AROMATIC COMPOUNDS

212. The name of these compounds has originated from the fact that the first substances in this class were discovered in constituents of plants characterised by a pleasant flavour or aroma.

In 1832 LIEBIG and WÖHLER examined the essential oil of bitter almonds; they found it contained a substance having the composition C_7H_6O , *benzaldehyde* (see 257), which may be oxidised to an acid $C_7H_6O_2$ *benzoic acid* (260). This acid was also found as a constituent of *gum benzoin*. In 1835, MITSCHERLICH found that by heating the calcium salt of benzoic acid with calcium hydroxide, a hydrocarbon C_6H_6 *benzene*, which had already been discovered in another way, (213) was produced.

A constituent of *tolu balsam*, *toluene* C_7H_8 , is also converted into benzoic acid on oxidation, so that it also is to be regarded as a derivative of benzene. In caraway-oil there occurs a hydrocarbon *cymene* $C_{10}H_{14}$, from which a dibasic acid, $C_8H_6O_4$, terephthalic acid (266), is produced on oxidation; on heating the calcium salt of this acid with calcium hydroxide, it is converted into benzene. Hence all the substances mentioned in these examples are to be regarded as derivatives of benzene.

Therefore, the term, *aromatic compounds*, has become a general one for a large class, which can be regarded as being derived from benzene in the same way as aliphatic compounds may be considered as derivatives of methane. The description "aromatic character" has therefore no reference now to the odour of the substances, but to the chemical properties of benzene and its derivatives.

(i) HYDROCARBONS OF THE BENZENE SERIES

213. These hydrocarbons form a homologous series the terms of which satisfy the general formula C_nH_{2n-6} . The second and successive terms of the series may be derived from benzene by replacing one or more of its hydrogen atoms by alkyl groups.

Thus these hydrocarbons contain 8 hydrogen atoms less than the corresponding alkanes with the same number of carbon atoms and should therefore

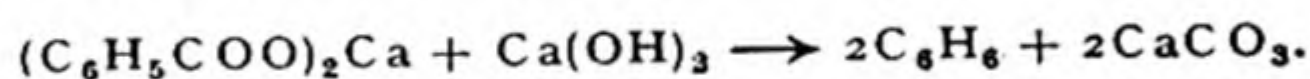
be considered, from their composition, as highly unsaturated compounds; their chemical properties, however, diverge considerably from those of the unsaturated aliphatic hydrocarbons. Hydrocarbons of the benzene series undergo addition reactions much less readily and are much less easily oxidised than alkenes or alkadienes.

When the hydrocarbons of the benzene series are compared with alkanes, there appears to be a characteristic difference in their behaviour towards strong nitric acid and fuming sulphuric acid. Alkanes, in general, do not react with these acids or only at elevated temperatures. Benzene and its homologues react with concentrated nitric acid or fuming sulphuric acid easily at ordinary temperatures; in both cases substitution products are formed without degradation of the hydrocarbon molecule occurring.

Benzene C_6H_6 was discovered by FARADAY in 1825 in a liquid obtained by compressing "oil-gas", but was first examined more closely sometime later. It occurs in small quantities in coal-tar, in which it was detected by A. W. VON HOFMANN in 1845 and from which it is now recovered commercially (see 219).

Benzene is a highly refractive liquid, which is very sparingly soluble in water; it is completely miscible with ether, ethanol and many other organic solvents.

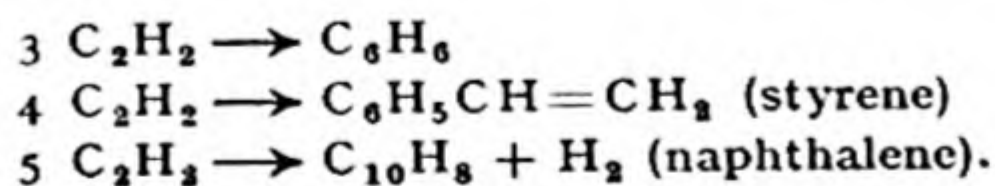
It is now obtained from coal-gas or coal-tar. It can be obtained in a pure state by heating calcium benzoate with calcium hydroxide:



When this reaction is carried out with the calcium salt of a homologue of benzoic acid, the corresponding homologue of benzene is produced.

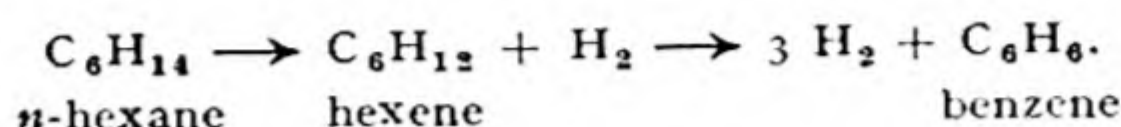
Modes of formation of benzene and its homologues from aliphatic hydrocarbons

The formation of benzene and other aromatic hydrocarbons, discovered by BERTHELOT, by heating ethyne to $700-750^\circ$, takes place more easily when the gas is passed over activated wood charcoal at 650° (ZELINSKY). A tar-like liquid is produced, which contains about 35 % of benzene along with toluene, *p*-xylene, styrene, naphthalene, etc.:

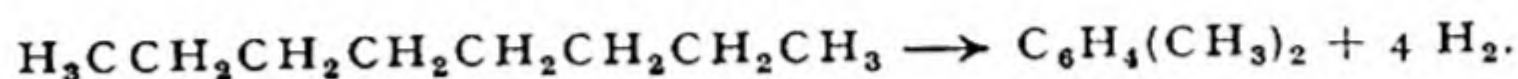


Toluene may also be produced in this reaction by the reductive decomposition of styrene with the simultaneous formation of methane. The polymerisation of ethyne to benzene can also take place at about 70° in a solvent, under the influence of special catalysts consisting of complex compounds of phosphines and nickel carbonyl (REPPE).

A very remarkable mode of formation of benzene and its homologues consists of the catalytic dehydrogenation of alkanes containing an unbranched chain of six carbon atoms. This reaction occurs at about 460° over a chromium oxide catalyst; four molecules of hydrogen are split off and a benzene ring is formed (MOLDAWSKY and KAMUSHER):



In a similar way toluene is produced from *n*-heptane and *o*-xylene from *n*-octane via octene-2:



The reaction product obtained in this process contains besides aromatic hydrocarbons and unchanged starting material, also considerable quantities of alkenes. This reaction is of importance for the "aromatisation" of aliphatic petrols, which results in an increased octane number. This "aromatisation" probably takes place via alkenes as intermediate products.

Chemical properties and structure of benzene. Nitrobenzene $\text{C}_6\text{H}_5\text{NO}_2$ (222) is produced by the action of nitric acid, and benzene sulphonic acid $\text{C}_6\text{H}_5\text{SO}_3\text{H}$ (227) by the action of sulphuric acid, on benzene.

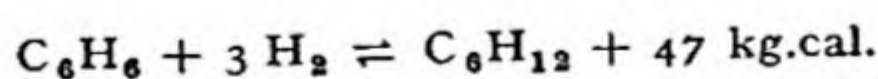
By the action of chlorine or bromine in the presence of halogen carrying catalysts, *e.g.* ferric halides, chloro- and bromo-benzene, respectively, are formed.

When the formula for benzene C_6H_6 is compared with that of hexane C_6H_{14} , the alkane with six carbon atoms, it is seen that benzene contains eight hydrogen atoms less than this saturated compound. It is obvious to assume therefore that polyvalent carbon bonds occur in benzene, as is the case in the alkenes, *e.g.* C_6H_{12} and the alkadienes *e.g.* C_6H_{10} .

Experience shows, however, that benzene is *not* oxidised by alkaline permanganate and that benzene does *not* decolourise bromine water, although under certain conditions six atoms of chlorine or bromine can add on to the molecule. Benzene hexachloride ($\text{C}_6\text{H}_6\text{Cl}_6$) is rapidly formed from a mixture of benzene and liquid chlorine in sunlight. Heat is set free in this reaction.

Four stereoisomeric benzene hexachlorides are produced, which differ in the relative positions of the chlorine and hydrogen atoms with regard to the carbon ring (VAN DER LINDEN). The γ -benzene hexachloride, melting at 113° , is an insecticide (LINDANE).

Benzene can add on six atoms of hydrogen and is converted into cyclohexane:



This reaction is reversible. At ordinary temperature the equilibrium lies on the side of cyclohexane, above 300° almost entirely on the side of benzene. The reduction takes place only in the presence of a catalyst, *viz.* active

platinum black at ordinary temperature or finely divided nickel at 180° (SABATIER and SENDERENS; WILLSTÄTTER; ZELINSKY).

Benzene can add on three molecules of ozone with the formation of a tri-ozonide which is split up into three molecules of glyoxal $\text{O}=\text{C}-\text{C}=\text{O}$ with water (HARRIES) (see p. 338).

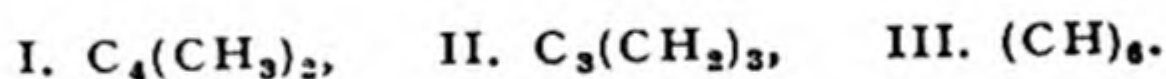
In these reactions benzene behaves like a substance with three double bonds, yet it deviates, as we have seen, from the behaviour of the unsaturated aliphatic hydrocarbons.

In order to establish how the six atoms of hydrogen are divided over the benzene molecule, two facts must be taken into account:

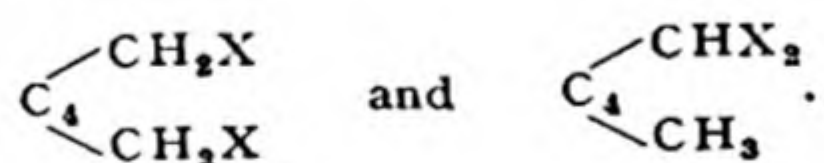
214. Firstly, *mono-substitution products of benzene do not occur in isomeric forms*. From this it follows, that the six atoms of hydrogen in benzene must be equivalent, *i.e.* whichever hydrogen atom is substituted, the same mono-substitution product is produced. For example, only one monobromobenzene $\text{C}_6\text{H}_5\text{Br}$, is known, one mononitrobenzene $\text{C}_6\text{H}_5\text{NO}_2$, one benzoic acid $\text{C}_6\text{H}_5\text{COOH}$, etc.

The second fact is that *di-substitution products can occur in three isomeric forms*. Thus three dibromobenzenes $\text{C}_6\text{H}_4\text{Br}_2$, for example, are known and are differentiated as *ortho*-, *meta*- and *para*-dibromobenzene.

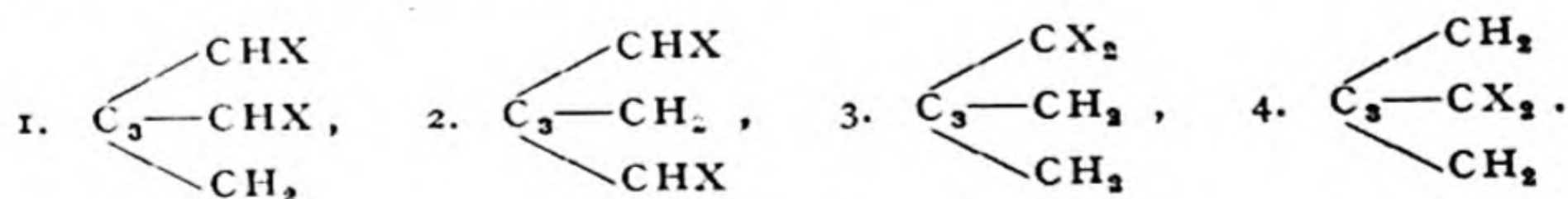
There are three possible formulae for C_6H_6 , in which all the six hydrogen atoms are equivalent:



If we now investigate which of these formulae is in agreement with the second requirement, we see that only two disubstitution products can be derived from formula I *viz.*:

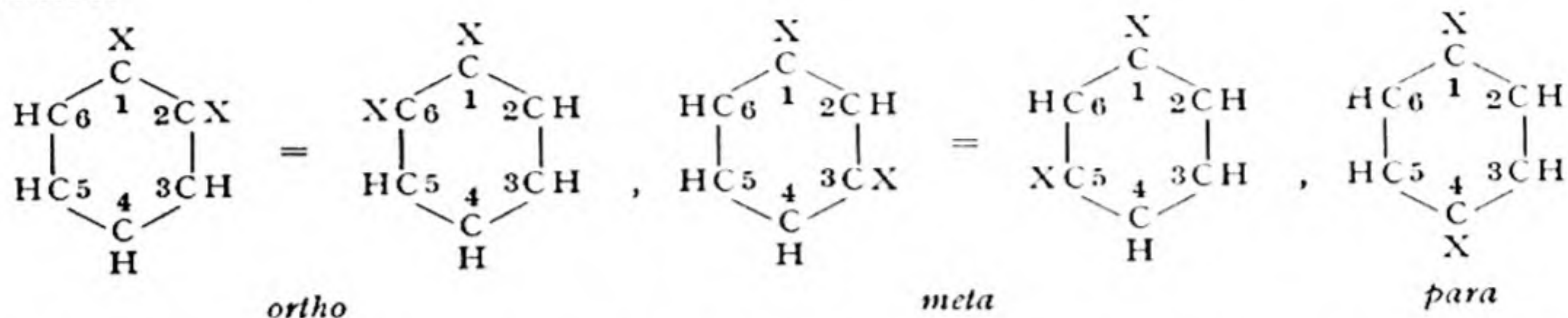


Hence this formula must be discarded. The following disubstitution products should be possible from II:

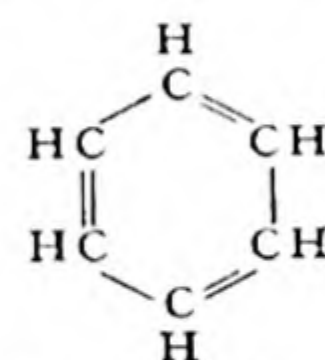


Of these, however, 1 is the same as 2 and 3 the same as 4, for the hydrogen atoms are equivalent and this can only be the case if the CH_2 groups also are exactly equivalent in the benzene molecule. According to formula II only two isomeric disubstitution products should be capable of existence, so that this formula also must be discarded.

Hence there remains formula III, in which *each of the carbon atoms carries one atom of hydrogen*. The carbon atoms of the benzene molecule cannot be arranged in an open chain, since in such a chain there are terminal and medial CH-groups, which are not equivalent. On the other hand, a *closed chain of six carbon atoms* fulfils the condition that *all the atoms of hydrogen are equivalent*. The cyclic formula at the same time fulfils the condition that three and not more than three isomers are possible in a disubstitution product.



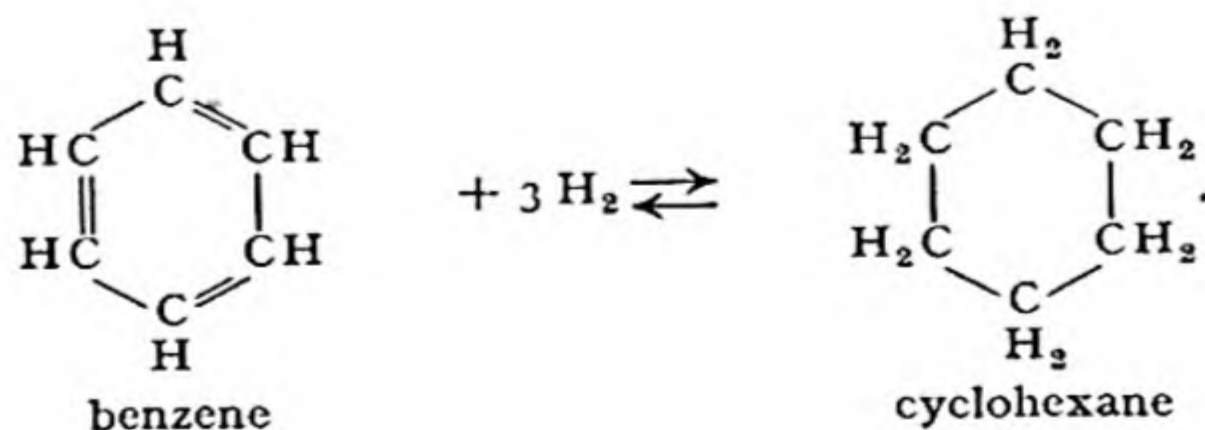
It is clear that the compounds $C_6H_4X_2$ 1,2 = 1,6 (*ortho*); 1,3 = 1,5 (*meta*) and 1,4 (*para*) are isomers. In the above schematic formulae each carbon atom is represented with three bonding forces. If the tetravalency of the carbon atom is maintained then the formula, which was suggested in 1865 by KEKULÉ and in which the carbon atoms are joined together alternately by single and double bonds, is obtained.

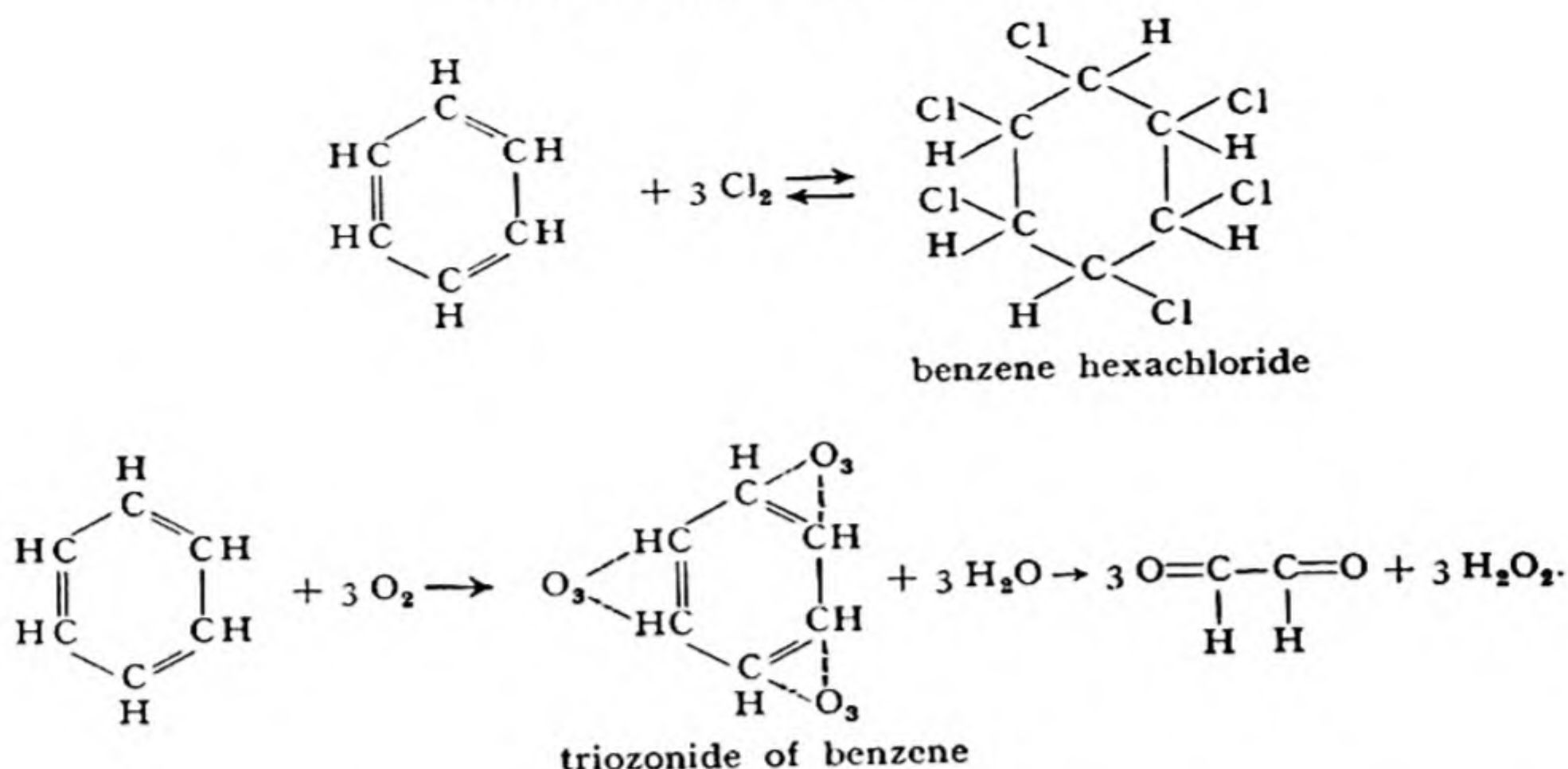


KEKULÉ'S
formula

KEKULÉ suggested this formula, because on supposition that the six atoms of hydrogen are equivalent, it appeared to him to be the simplest and there were no known facts which were opposed to this hypothesis. Also, at the same time, he took the tetravalency of the carbon atoms as his basic starting point. It followed from KEKULÉ's formula, that disubstitution products must occur in three isomeric forms. In 1865, however, only two isomers were known of many disubstituted products, so that KEKULÉ could make no use of the experimental data then available to prove the correctness of his formula. In succeeding years, however, the conclusions which may be drawn from this formula, were amply confirmed by the work of a very large number of investigators. The addition of hydrogen and the formation of a tri-ozonide, from which the presence of three double bonds may be deduced, were first accomplished at the beginning of the present century. The KEKULÉ formula therefore has become the basis for the theory of structure of aromatic compounds and thereby also for the theory of cyclic compounds in general.

The addition reactions of benzene are therefore represented by the following formulae:





The space model of the benzene molecule must fulfil the condition that the carbon atoms lie in a plane with the atoms of hydrogen, since any other spatial configuration would lead to the occurrence, for *ortho*- and *meta*-disubstituted products, of incongruent mirror images and hence to the possibility of optical activity, not a shred of evidence for which has ever been found. This condition is fulfilled by the KÉKULÉ formula.

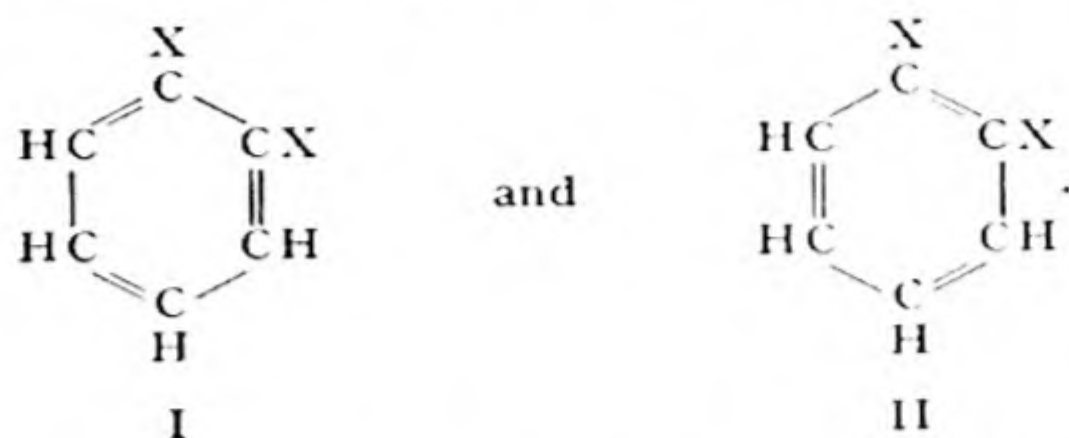
The planar structure of the benzene ring is confirmed by the X-ray examination of the crystal structure of hexamethylbenzene $\text{C}_6(\text{CH}_3)_6$, from which it follows: firstly, that the carbon atoms of the benzene ring lie in a plane, in which the carbon atoms of the CH_3 -groups are also situated, secondly, that the distances between two successive carbon atoms (sides of the hexagon) are all the same and equal to 1.39 Å and thirdly, that the molecule possesses a centre of symmetry (LONSDALE, 1929).

The equivalence of the C—C bonds in benzene follows also from researches on the infra-red and Raman spectra of benzene compared with those of a benzene in which some of the atoms of hydrogen have been replaced by atoms of deuterium (INGOLD).

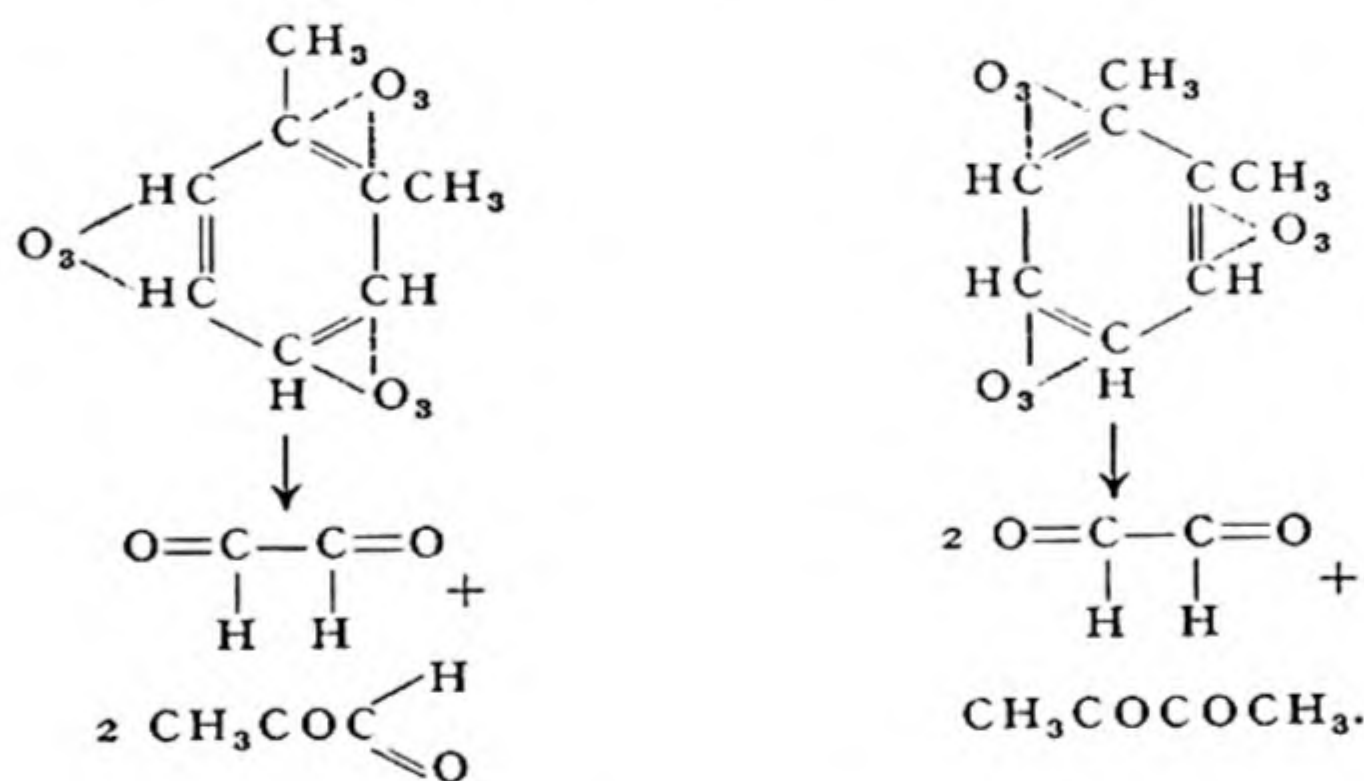
These results are not in agreement with a model of the KÉKULÉ formula, since in this the sides of the hexagon should have alternating lengths of 1.54 Å (C—C distance) and 1.34 Å (C=C distance) (compare 37); this figure does not possess a centre of symmetry. Hence there is a discrepancy between the results of chemical researches, on the grounds of which we must assume that benzene can react like a substance with double bonds, and of physical investigations, from which it follows that no double bonds are present in the benzene molecule. It will be apparent from the following how both opinions can be reconciled.

215. According to the KÉKULÉ formula two isomeric forms should be

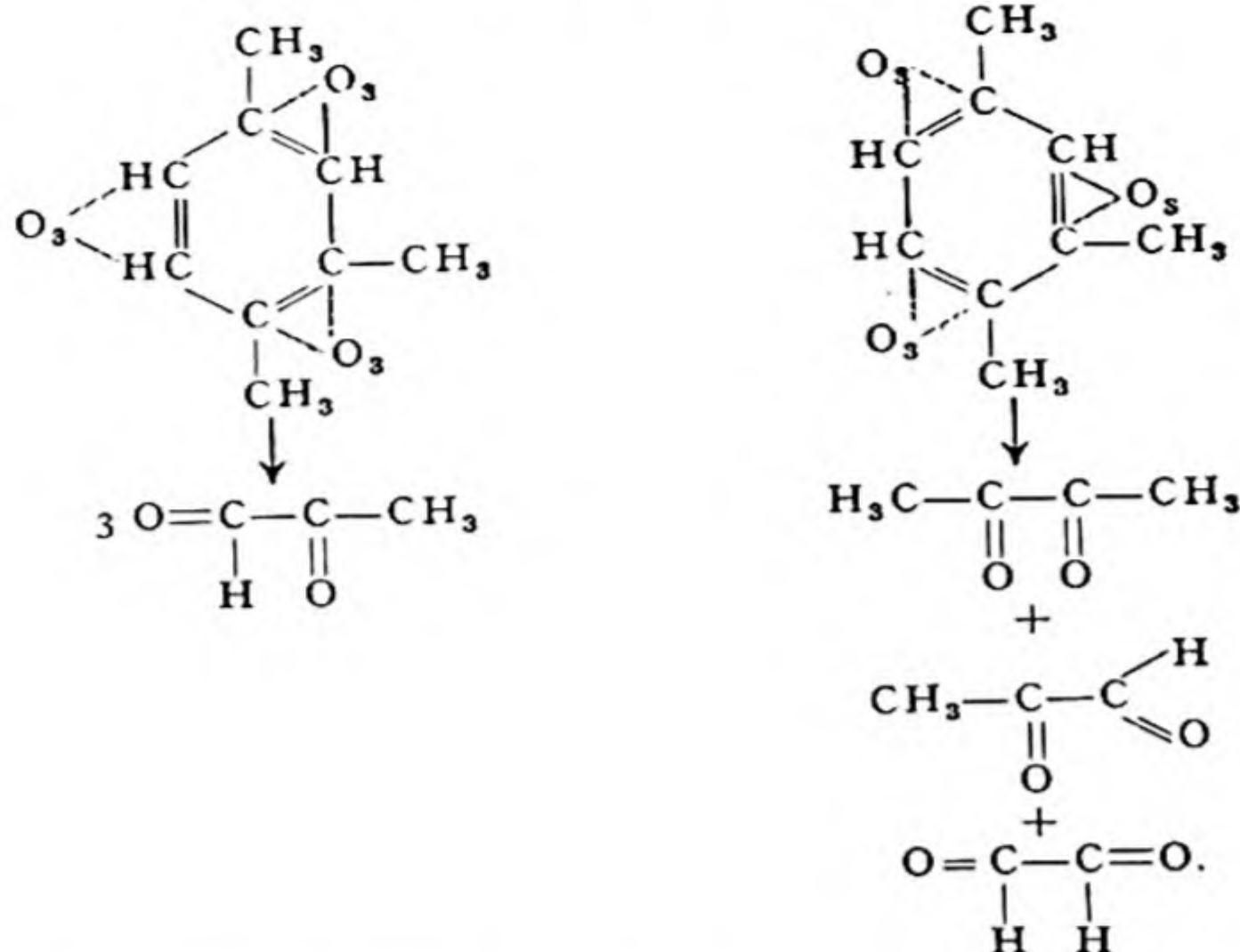
possible for *ortho*-disubstitution products, since the carbon atoms which carry the two substituents may be joined by either a single or a double bond:



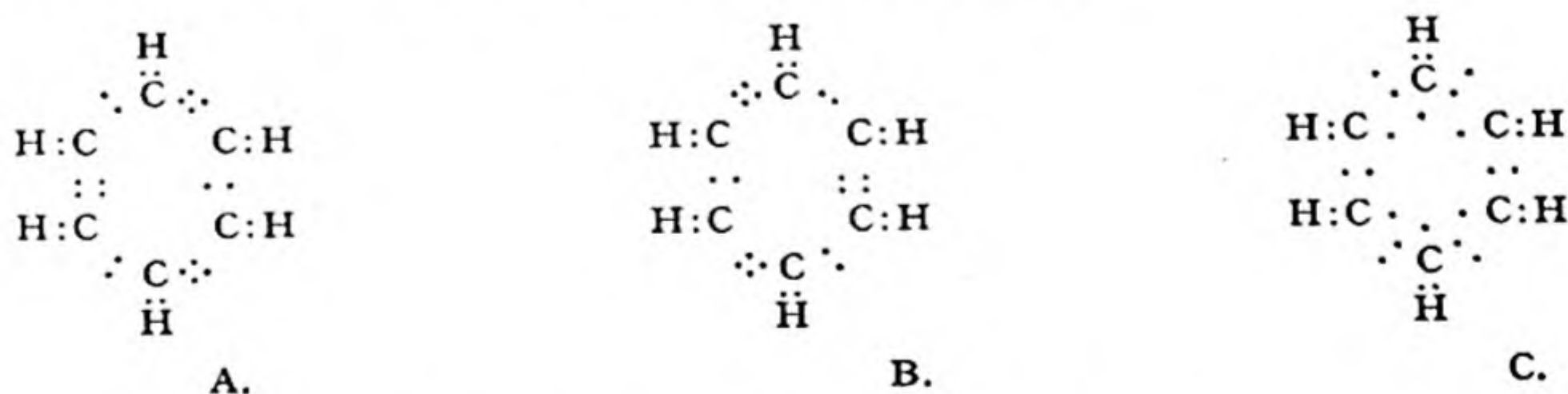
Since no observations have ever been made which would point to the existence of isomeric *ortho*-derivatives, it is assumed, in accordance with a hypothesis put forward by KEKULÉ in 1869, that the double and single bonds in the benzene ring can rapidly exchange places with each other, so that the above mentioned *ortho*-derivative must be represented by both the structures I and II, which are rapidly converted one into the other. Confirmation of this hypothesis was provided in 1932 by LEVINE and COLE, who showed that by the action of ozone on *o*-xylene and decomposition of the triozone formed, three oxidation products were produced, namely, glyoxal, methylglyoxal and diacetyl (146). These three compounds can be produced if the xylene reacts according to both KEKULÉ structures, as appears from the formulae given below:



Since the chance of reaction is equally great for each of the KEKULÉ structures, the decomposition products mentioned above should be formed in the ratio of 1 mol. of diacetyl : 2 mols. of methylglyoxal : 3 mols. of glyoxal. From an investigation by WIBAUT and HAAYMAN it follows that this is indeed the case. The same oxidation products are produced in the ozonisation of 1,2,4-trimethylbenzene in the ratio of 1 mol. of diacetyl : 4 mols. of methylglyoxal : 1 mol. of glyoxal. Hence 1,2,4-trimethylbenzene reacts according to both KEKULÉ structures in equal measure:



The two KEKULÉ structures of the benzene molecule differ only in the arrangement of the valency electrons; the atomic nuclei occupy the same position in both structures (electron configurations A and B). From wave-mechanics it follows that a molecule, for which two structures can be set up differing only in the arrangement of the valency electrons, actually assumes a structure, in which the distribution of the valency electrons lies in between those of the two limiting structures. This is designated as *resonance between valency structures* or, following a suggestion by INGOLD, as *mesomerism* (i.e. "between the parts"). In this structure (configuration C) two valency electrons are found between each pair of carbon atoms. Each carbon atom has an unshared valency electron and it is assumed that these six valency electrons arrange themselves in a group of six. Calculation shows that this configuration is more stable energetically than either of the configurations A or B (L. PAULING; E. HÜCKEL).



It is clear that in configuration C the distances between successive carbon atoms is the same in all cases and that this configuration has a centre of symmetry.

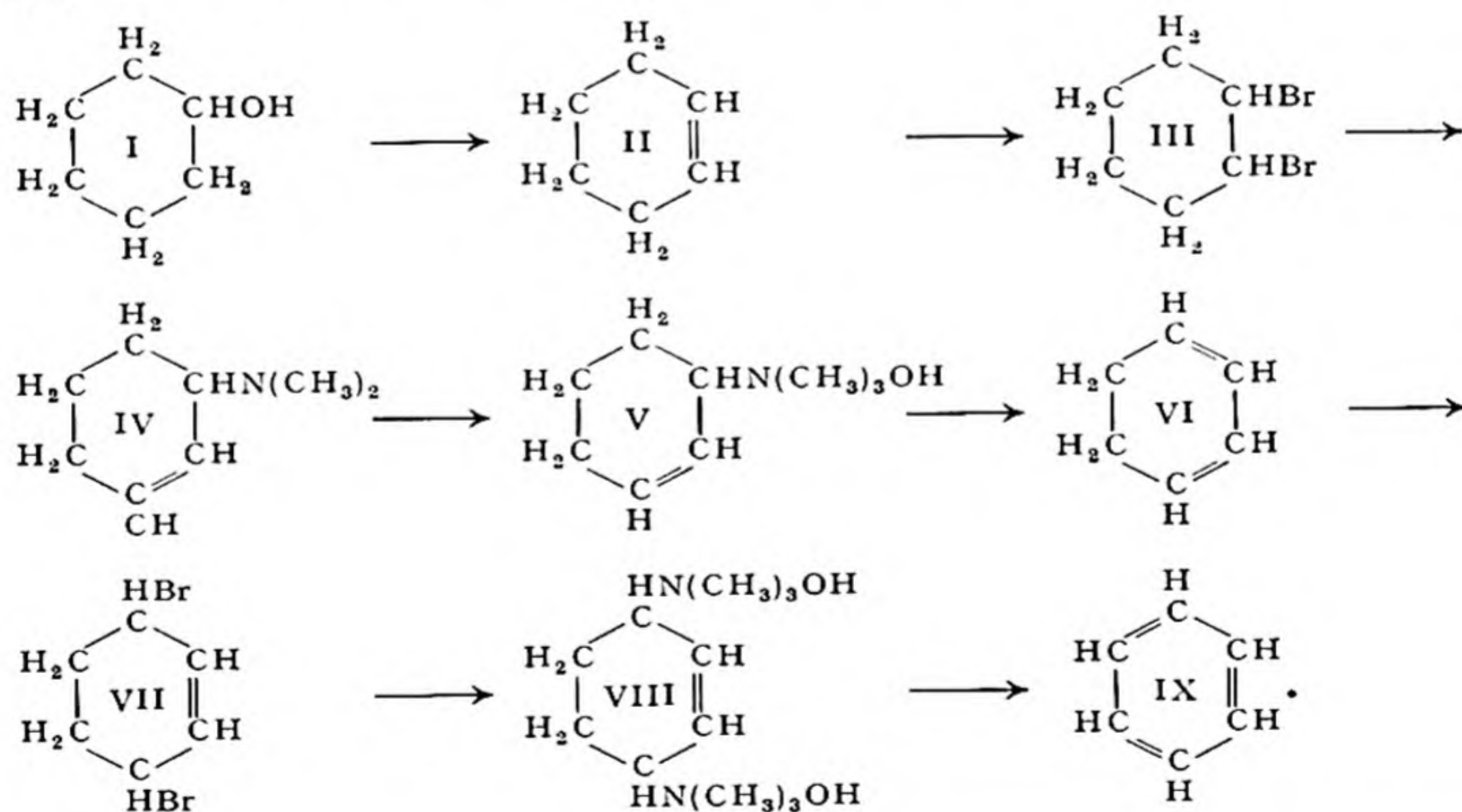
The idea of mesomerism is to be clearly differentiated from tautomerism (149). In the conversion of tautomeric forms into one another, not only is

there a displacement of the valency electrons but also a simultaneous displacement of a proton. Benzene or a derivative of benzene is not to be regarded as a mixture of two KÉKULÉ forms which change into one another in the manner of tautomers. The benzene molecule in its condition of rest is an intermediate form between the two limiting KÉKULÉ structures in which the C—C bonds in the ring are mutually equivalent.

In addition reactions of benzene—which are preceded by an activation of the molecule—accompanied by a transfer of energy—benzene reacts like a substance with three double bonds in accordance with both the KÉKULÉ structures, this, as we have already seen, can be demonstrated in an appropriately chosen example.

216. The typically aromatic character will not be evident therefore in a six ring system with one or two double bonds in the ring, since in these cases a mesomeric form is not possible. This is clearly apparent from the properties of *cyclohexene* C_6H_{10} and *cyclohexadiene* C_6H_8 , which behave like unsaturated open-chain hydrocarbons.

Cyclohexene, II, which can easily be obtained by splitting off water from cyclohexanol, I, behaves like an unsaturated compound and easily adds on two atoms of bromine:



In order to prepare cyclohexadiene from this dibromocyclohexane it is warmed with dimethylamine, when a molecule of hydrogen bromide is split off and a bromine atom is replaced by the $-N(CH_3)_2$ group, so that the unsaturated tertiary base, IV, is produced. This cyclohexenylamine is now treated with methyl iodide and then with silver hydroxide, by which means base V is produced; this is converted into cyclohexadiene (VI) by dry distillation under reduced pressure. Both II and VI behave

like unsaturated compounds and are, for example, oxidised by dilute alkaline permanganate solution. When bromine is added to VI, VII is produced (see 92), which can be converted into the diammonium base, VIII, like III into V. At a pressure of 0.01 mm. this base decomposes even at 0° into water, trimethylamine and cyclohexatriene (IX) which is identical with benzene. As soon as a third double bond is introduced into the six-ring, a substance with aromatic characteristics is produced (WILLSTÄTTER, 1912).

Cyclo-octatetraene. In a similar way, by degradation of the alkaloid pseudo-pelletierene, in the molecule of which a cyclo-octane ring occurs, WILLSTÄTTER obtained a hydrocarbon of the composition C_8H_8 , *cyclo-octatetraene*. He assigned structure I (below) to this compound, because on reduction it took up eight atoms of hydrogen with the formation of cyclo-octane. From recent investigations by REPPE it appears that cyclo-octatetraene can be prepared by the polymerisation of ethyne under the influence of specific catalysts. For this purpose, acetylene at a pressure of 10–15 atmospheres and a temperature of about 100° is led into a suitable solvent, preferably tetrahydrofuran, in which nickel cyanide is suspended.

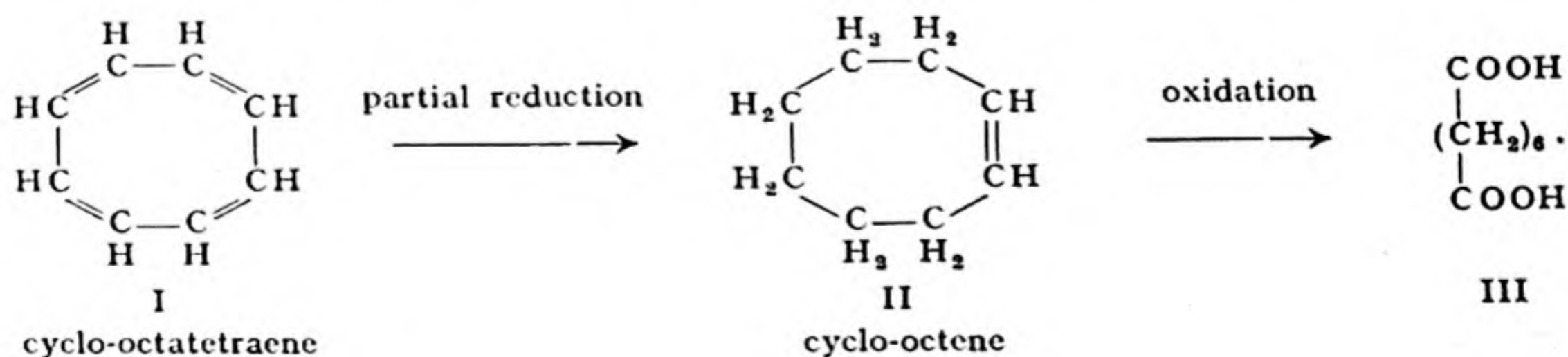
Cyclo-octatetraene is a golden yellow liquid, which boils at 142°; setting point -7° , d_4^{20} 0.925, n_D^{20} 1.5389. The molecular heat of combustion amounts to 1084.7 kcal, from which it follows that the heat of formation from graphite and hydrogen is -59 kcal. (ROSSINI).

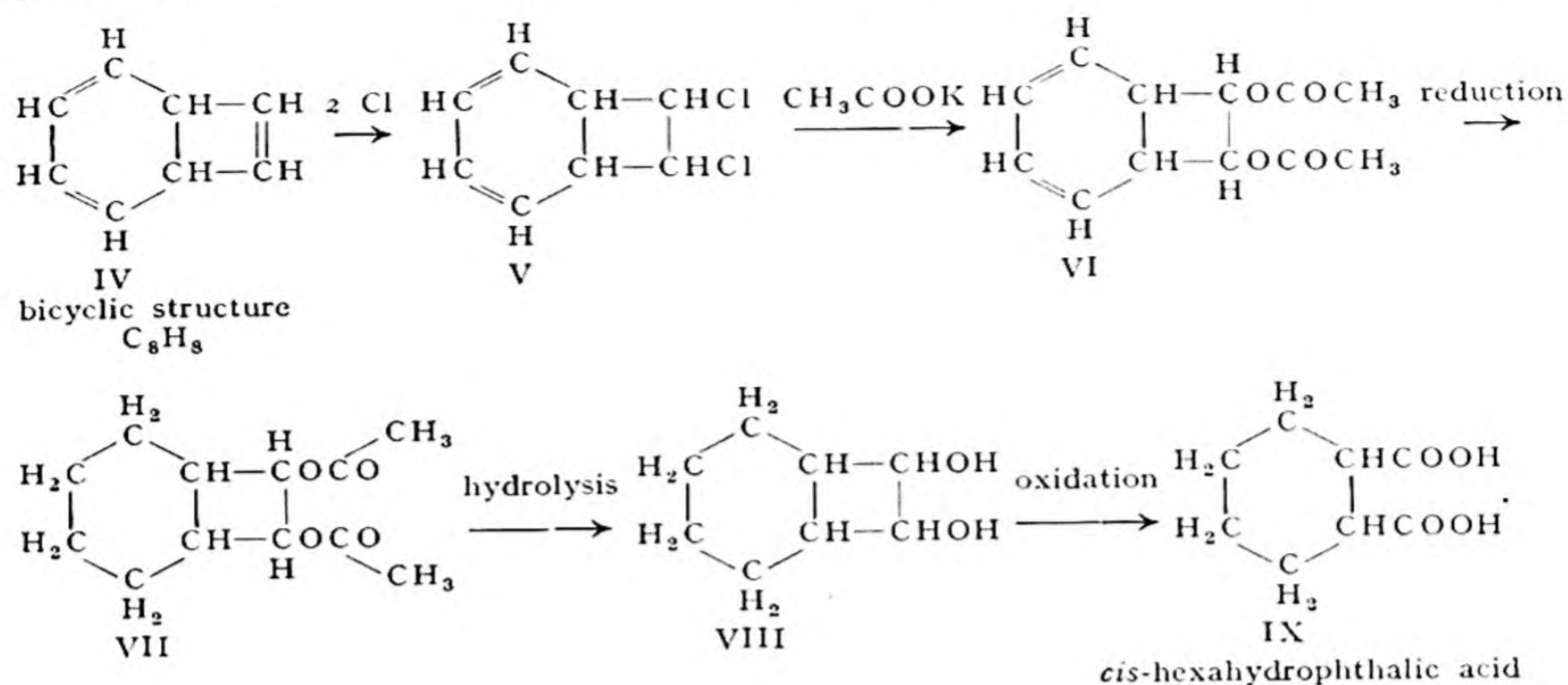
Cyclo-octatetraene has powerful unsaturated properties; it is quickly oxidised by permanganate dissolved in glacial acetic acid and is slowly attacked by atmospheric oxygen. By the action of a mixture of sulphuric acid and nitric acid, nitration does not take place but resinous products are produced.

The Raman spectrum of cyclo-octatetraene indicates that the carbon ring has a non-planar structure. Consequently, the occurrence of mesomerism, which would be expected with a planar structure, is impeded. This is related to the fact that cyclo-octatetraene has an unsaturated character compared with benzene.

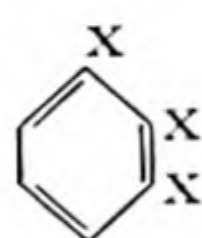
The catalytic reduction of cyclo-octatetraene can also be carried out in such a way that cyclo-octene (II) is produced as the chief product, from which suberic acid (III) (124) is obtained by oxidation with permanganate. This observation is in accordance with formula I.

REPPE and his collaborators have found, however, that this remarkable hydrocarbon can undergo various reactions in which it reacts as a bicyclic structure (IV). By the action of sulphuryl chloride (SO_2Cl_2) two chlorine atoms are added to the molecule and a dichloride $C_8H_8Cl_2$ is produced. Structure V is assigned to this compound on the basis of the following reactions. The chlorine atoms can be replaced by acetoxyl groups by the action of potassium acetate; the ester VI so obtained, is converted by catalytic reduction into VII, from which a diol (VIII) is obtained by hydrolysis. *cis*-Hexahydrophthalic acid (291) is produced by oxidising this diol with nitric acid:

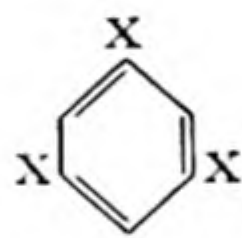




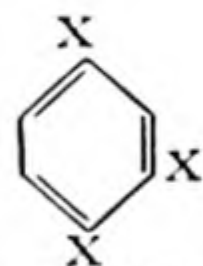
217. Nomenclature and isomerism of benzene derivatives. It has already been said that the number of isomeric disubstitution products, denoted by the prefixes *ortho*-, *meta*- and *para*-, or by the numerals 1,2-, 1,3- or 1,4-, is the same for similar or dissimilar substituents. This is not the case for three substituents. If the substituents are alike, there are three isomers:



vicinal
1,2,3-



symmetrical
1,3,5-



asymmetrical
1,3,4-

If one substituent is different from the two others, there is a difference according to whether this substituent stands in the 2- or 3- position in the vicinal derivative or in the 1-, 3- or 4-position in the asymmetrical compound.

The number (10) of isomers with three dissimilar groups can be derived quite easily. With four similar substituents in the nucleus the same number (3) of isomers is formed as with two, since the remaining two atoms of hydrogen may be situated in the *ortho*-, *meta*- or *para*-position to each other.

If an alkyl or similar group is attached to the benzene nucleus such as in C₆H₅CH₃, C₆H₅CH₂CH₂CH₃ or C₆H₅CH₂OH, these are termed *side-chains*. The ring of six carbon atoms is frequently termed the *benzene nucleus*. Substituents may occur in both nucleus and side-chain. The group C₆H₅- is called the *phenyl group*.

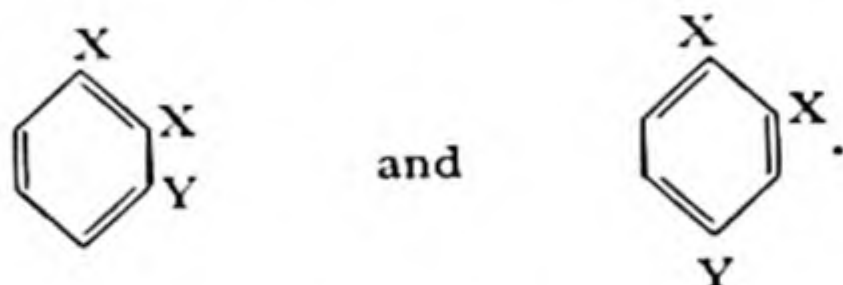
At one time GERHARDT (1837) suggested the name *phene*, derived from the Greek verb to shine (φαίνειν), for the hydrocarbon which we now call benzene, since benzene burns

with a bright luminous flame. This name never came into general use, however, but the terms *phenyl-group* and *phenol* (229) are derived from it.

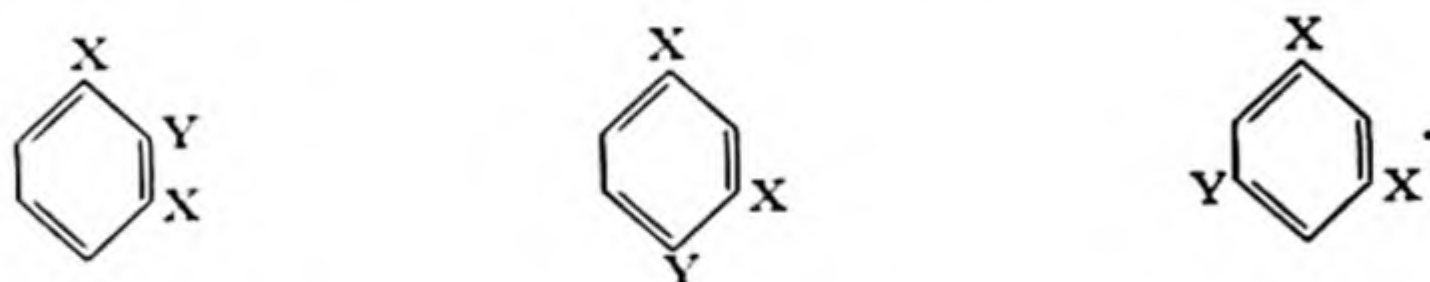
Following the rule that unsaturated hydrocarbons are denoted by the suffix *ene* the name benzene is formed from the earlier common name in general use for this substance, *benzol*. The name benzol was chosen by MITSCHERLICH, because he obtained the hydrocarbon C_6H_6 from benzoic acid, which derived its name from gum benzoin.

The establishment of the actual carbon atoms in the benzene nucleus to which particular substituents are attached, is known as the *determination of position or the orientation of substituents*. The methods used for this purpose are based on the following principles.

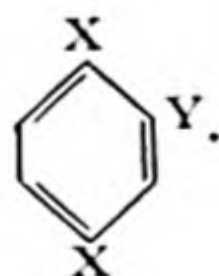
1st Absolute orientation. A general method is known as KÖRNER's principle (1874), by which disubstitution products with similar substituents, $C_6H_4X_2$, are identified as *ortho*-, *meta*- or *para*-compounds, by investigating how many trisubstitution products can be produced from them. If a third group Y (similar or dissimilar to X) is introduced into an *ortho*-compound, then according to KEKULÉ's formula *two* isomers may be produced:



In a *meta*-compound, *three* isomers can be formed when a third substituent is introduced:



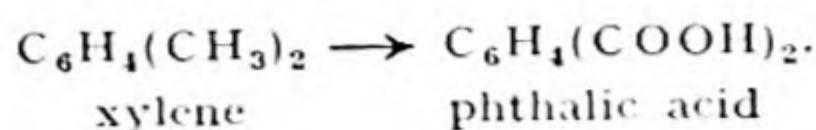
Only *one* trisubstitution product can be produced by the introduction of a third group into a *para*-compound:



Later on we shall discuss examples of orientation by KÖRNER's principle (271).

2nd Relative orientation. In this method an attempt is made to convert compounds in which the positions of the substituents are unknown, into compounds in which these are known, it being reasonable to conclude, that the substituents in the first compound occupy the same positions as in the compounds, which have been derived from it. For example, if it is desired

to determine the structure of *o*-, *m*- or *p*-xylene the hydrocarbon may be oxidised to the benzene dicarboxylic acid (266):

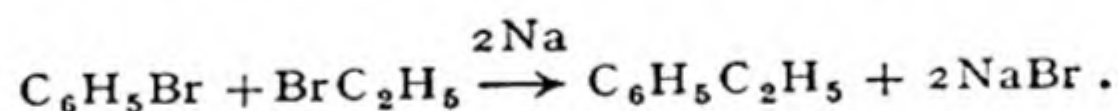


If the position of the carboxyl groups in the three phthalic acids is known, then the position of the methyl groups in the xylenes follows. In order to apply this method the position of the substituents for a number of compounds must be definitely known. Further, it is assumed that the substituents do not change place during the various reactions. Experience has shown that this assumption is justified in most cases. Examples are known, however, [see bromobenzenesulphonic acids (227)], in which a substituent changes its position. Sometimes, when a compound containing a sulphonic acid group is fused with potash to replace the sulpho group by hydroxyl, the latter enters another position. Any uncertainty in the determination of position is removed when, as is done in many cases, another synthetic method is used. The connexion between di- and tri-substitution products derived from the formula of KEKULÉ has been thoroughly confirmed by countless experiments since the formula was put forward.

218. Homologues of benzene. *Toluene*, $\text{C}_6\text{H}_5\text{CH}_3$, occurs along with benzene and other homologues in coal-tar and is obtained commercially from this material (219).

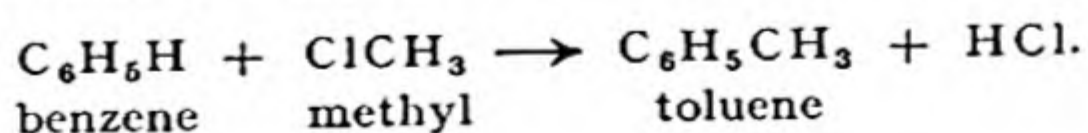
Preparation of alkylbenzenes

1. By the *FITTIG synthesis*. In this reaction an alkyl bromide (or iodide) and sodium are allowed to interact with bromobenzene or, more generally with a nuclear brominated aromatic hydrocarbon:

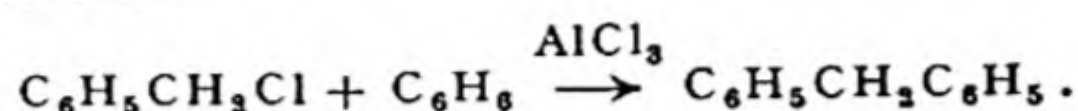


This reaction is similar to the synthesis of alkanes from alkyl halides by the method of WURTZ (17). By-products like diphenyl $\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_5$, (273) and the corresponding dialkyls are frequently formed in the FITTIG synthesis. A good yield of alkylbenzene is obtained when the higher normal primary alkyl iodides are used.

2. By the *synthesis of FRIEDEL and CRAFTS*, which is specific for the aromatic series. This method depends on a peculiar property of aluminium chloride; when this substance is introduced into a mixture of an aromatic hydrocarbon and an alkyl chloride, hydrogen chloride is evolved and a hydrogen atom in the benzene nucleus is substituted by an alkyl group:



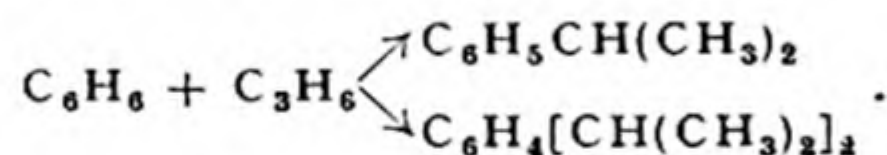
This equation gives a simplified view of the reaction, which is actually rather complicated. Addition compounds can be formed of aluminium chloride with the aromatic hydrocarbon, with the alkyl halide and with the homologue of benzene formed in the reaction (BÖESEKEN). These addition compounds are usually produced from 1 mol. of aluminium chloride and 1 mol. of the substances mentioned. If the aluminium chloride is not fixed by the formation of an addition compound, only a small amount is necessary, *e.g.* in the synthesis of diphenylmethane (273) from benzyl chloride (221) and benzene:



This reaction takes place quite readily on the addition of 1/50th of a mol. of aluminium chloride. On the other hand, *p*-nitrobenzyl chloride gives an addition compound with aluminium chloride so that 1 mol. of the latter must be used in the synthesis of *p*-nitrodiphenylmethane $\text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_4\text{NO}_2$, (BÖESEKEN); it is assumed that this addition compound dissociates to a small extent and that the uncombined aluminium chloride is the actual catalyst in the FRIEDEL-CRAFTS synthesis.

By this method, the reaction does not as a rule stop when one alkyl group has been introduced, a mixture of mono- and higher substitution products is usually produced so that fractional distillation must be carried out after the synthesis to separate the homologues. Also the breaking down of hydrocarbons may be observed as well as their synthesis. If toluene $\text{C}_6\text{H}_5\text{CH}_3$, for example, is treated with aluminium chloride, both benzene C_6H_6 and xylene $\text{C}_6\text{H}_4(\text{CH}_3)_2$ are produced. Hence the alkyl groups are transferred from one molecule to another.

3. By the action of alkenes on benzene in the presence of condensing agents like sulphuric acid, phosphoric acid, aluminium chloride, etc., a mixture of mono-, di- and tri-alkylbenzenes is produced according to the scheme:



During this reaction part of the alkene is condensed to higher alkenes (87).

TABLE 40

SOME PHYSICAL CONSTANTS OF BENZENE AND ITS HOMOLOGUES

Name	Formula	Boiling point °C	Refractive index n_D^{20}	Melting point °C	Heat of combustion kg.cal./mol. 25° const. pressure	Spec. grav. d_4^{20}
Benzene	C_6H_6	80.07	1.5010	5.49	780.98	0.8790
Toluene	$\text{C}_6\text{H}_5\text{CH}_3$	110.56	1.4962	—95.18	934.50	0.8665
<i>m</i> -Xylene	$1,3-\text{C}_6\text{H}_4(\text{CH}_3)_2$	139.08	1.4972	—47.87	1087.9	0.8642
Mesitylene	$1,3,5-\text{C}_6\text{H}_3(\text{CH}_3)_3$	164.74	1.4994	—44.82	1241.21	0.8637
Ethylbenzene	$\text{C}_6\text{H}_5\text{C}_2\text{H}_5$	136.06	1.4959	—94.97	1091	0.8670
Isopropylbenzene (cumene)	$\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)_2$	152.39	1.4915	—96.7	1246.51	0.8623
1-Methyl-4-iso- propylbenzene (cymene)	$\text{C}_6\text{H}_4 \begin{cases} \nearrow \text{CH}_3 (1) \\ \searrow \text{CH}(\text{CH}_3)_2 (4) \end{cases}$	176.9	1.4903	—69.8	1400	0.8573

Physical properties. The homologues of benzene are colourless liquids at room temperatures with strong refractive properties and a characteristic odour. They are miscible in all proportions with anhydrous methanol, ether and many other organic solvents but they are immiscible with water. Some of their physical constants are given in Table 40.

Occurrence of aromatic hydrocarbons in nature and in industrial products

219. Benzene and some of its homologues occur in certain kinds of petroleum, *e.g.* in Borneo oil. *Cymene*, $C_{10}H_{14}$, 1-methyl-4-isopropylbenzene, occurs in some essential oils such as *Italian camomile-oil*, *caraway-oil*, *thyme-oil* and *eucalyptus-oil*. It is obtained in large quantities in the preparation of cellulose by the sulphite method (190), it being derived from the terpenes (294) which are present in wood (pine).

Coal-tar and coal-gas form the chief source of aromatic hydrocarbons.

Carbonisation of coal; the tar. The carbonisation (dry distillation) is carried out in retorts or furnaces of fire-brick heated to a temperature of 1000–1200°. Coal-gas, *i.e.* a mixture of hydrogen, methane, hydrocarbons and carbon monoxide (illuminating gas manufacture) is produced along with coke, which is also manufactured on a large scale in coke-ovens for the iron and steel industries. The yield of coke, a hard, black mass, consisting mainly of carbon along with small amounts of mineral constituents, amounts to about 70 % of the weight of coal carbonised. Coal-tar is produced as a by-product in a yield of about 4 %.

The elementary composition of coal used in the manufacture of coke and gas—omitting the mineral constituents—is about 88–91 % C, 4.5–5.5 % H, 4.5–5.5 % O, 1 % N and 1–2 % S. Carbon is not present in the free state in coals; it exists as a mixture of organic compounds of high molecular weight, which has so far evaded all attempts to separate it into its constituents. The main component of coal consists of humus-like substances, black masses formed from the lignin and the cellulose of the vegetable remains, from which coal is formed. Lean coals, like anthracite, consist almost completely of these substances.

Bituminous coals, however, contain, in addition, bituminous constituents—produced from vegetable resins or from humic acids—which may be isolated by extracting the coal with benzene or pyridine. This *bitumen* produces the tar on thermal decomposition. When the dry distillation of coal is carried out at about 450°, *e.g.* by working under reduced pressure, a tar of quite different composition is produced (PICTET). This *primary tar* or *vacuum tar* contains practically no aromatic hydrocarbons but hydro-aromatic hydrocarbons and, in addition, homologues of phenol. By heating to about 900° the primary tar is decomposed and a tar is produced similar in character to that from gas-works and coke-ovens. Hence the formation of ordinary coal tar takes place in two stages. At low temperatures the above-mentioned substances are formed from the bitumens in the coal and at higher temperatures they are split up into aromatic compounds and gaseous products.

The tar is a thick black liquid (containing suspended particles of carbon)

with a characteristic odour and consists of a mixture of acid, basic and neutral substances. The latter are chiefly hydrocarbons belonging for the greater part to the aromatic series. Benzene and toluene are present to the extent of 1–1.5 %; naphthalene (279) to the extent of 5–10 %.

Of the acid constituents, *carbolic acid* or *phenol* is the most important. The basic constituents are present only in small amounts and include pyridine, quinoline and their homologues as well as ammonia which remains dissolved in the water present in the tar.

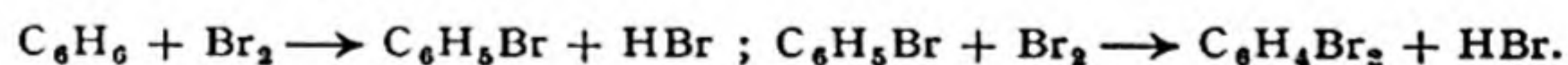
These constituents of the tar can be separated by distillation, leaving a thin black mass behind in the still; this is the *pitch*. The following fractions are usually separated from the distillate:

1. *Light tar oil* boiling below 180°.
2. *Carbolic oil*, boiling at 180–230°.
3. *Heavy tar oil* or *creosote oil*, boiling at 230–280°.
4. *Anthracene oil* boiling above 280°.

The light tar oil contains benzene and its homologues, which can be separated from one another by fractionation. The chief homologues are *toluene* or methylbenzene and *xylene*s or dimethylbenzenes, the *meta*-compound predominating. Small quantities of benzene vapour occur in crude coal-gas (coke-oven gas), from which it can be removed by washing with heavy tar oil, the benzene subsequently being recovered by distillation. Benzene is obtained in this way on a large scale as a by-product from coke manufacture.

(ii) HALOGEN SUBSTITUTION PRODUCTS OF BENZENE AND ITS HOMOLOGUES

220. Mono-halogeno-substitution products of benzene. The action of chlorine or bromine on benzene in the presence of halogen carrying catalysts like ferric chloride or bromide, antimony chloride or aluminium chloride, leads to the replacement of one or more atoms of hydrogen in the benzene nucleus by halogen atoms. In this way there are produced not only mono-halogenobenzenes but also di- and tri-substitution products according to the quantity of halogen used:



For the preparation of bromobenzene, bromine is added with cooling to benzene containing a few iron turnings; a brisk reaction takes place and hydrogen bromide is evolved.

Iodine does *not* react with benzene at ordinary temperatures; in order to prepare iodobenzene by direct iodination, benzene must be heated with iodine and iodic acid in a sealed tube. The iodic acid serves to oxidise the hydriodic acid produced to iodine, since otherwise it would favour the

reversible reaction in which the iodine atom in iodobenzene is replaced by an atom of hydrogen.

If a mixture of benzene vapour and gaseous fluorine diluted with nitrogen is passed over copper gauze at 90° , there is produced as chief product *dodecafluorocyclohexane* C_6F_{12} (b.p. 52°). At the same time degradation occurs with the production of lower carbon fluorides including CF_4 , C_2F_6 , C_3F_8 (FUHUKARA and BIGELOW).

A method is described in 246 for preparing mono-halogenobenzenes from aminobenzenes.

Properties. Some of the physical constants of the mono-halogeno-substitution products of benzene are collected together in Table 41.

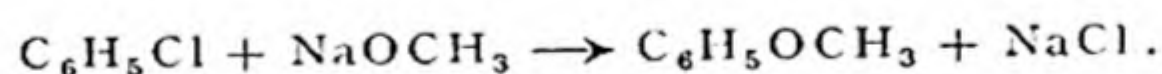
TABLE 41

SOME PHYSICAL CONSTANTS OF THE MONO-HALOGENO-SUBSTITUTED BENZENES

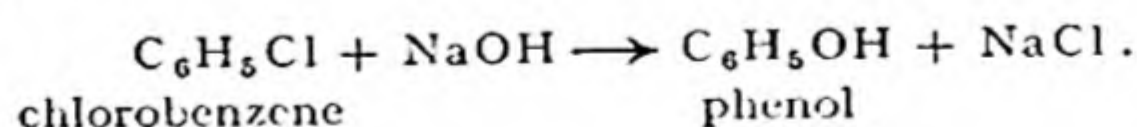
Name	Formula	Boiling point $^\circ C$	Setting point $^\circ C$	Spec. grav. d_4^{20}	Refractive index n_D^{20}
Mono-fluorobenzene	C_6H_5F	85.2	-40.5	1.0236	1.4677
Mono-chlorobenzene	C_6H_5Cl	132	-45	1.1064	1.5251
Mono-bromobenzene	C_6H_5Br	156.15	-30.6	1.4953	1.5600
Mono-iodobenzene	C_6H_5I	188.55	-31.35	1.8325	1.6189

The mono-halogenobenzenes are colourless liquids. Iodobenzene becomes dark brown in colour when exposed to light on account of the separation of iodine.

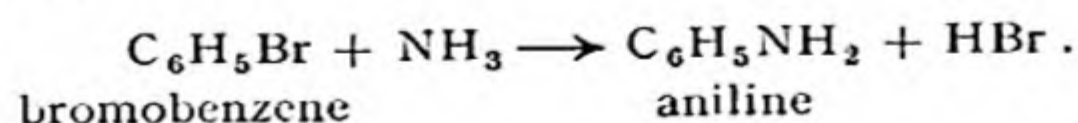
The halogen atom in the mono-halogenobenzenes is unreactive. These compounds can be boiled in aqueous or alcoholic solutions of alkalis, potassium hydrosulphide or potassium cyanide without replacement of the halogen atom occurring. When the mono-halogenobenzenes are heated with sodium methylate to 220° , the halogen atom is replaced by the methoxyl group:



The halogen atom is replaced by the hydroxyl group by heating with caustic soda at 300° :



Aniline (236) is produced by heating chloro- or bromo-benzene with aqueous ammonia under pressure to about 200° in presence of a little copper sulphate as catalyst:

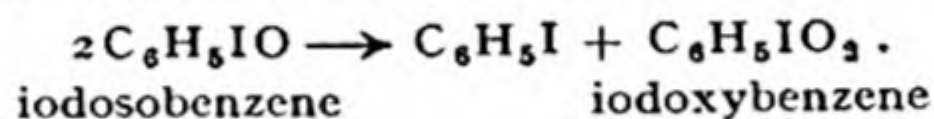


The reactivity of the halogen atoms in halogenobenzenes is comparable with the reactivity of the halogen atoms in the halogenoalkenes, in which the halogen atom is attached to the carbon atom carrying the double bond. In two cases, however, reaction takes place readily, namely, in the FITTIG synthesis (see 218) and the GRIGNARD reaction.

Magnesium reacts with bromobenzene in dry ethereal solution to form phenylmagnesium bromide, C_6H_5MgBr , as easily as it does with an alkyl halide (39). This compound can be used to prepare tertiary alcohols containing a phenyl group in the same way as tertiary aliphatic alcohols are prepared (77).

Compounds with iodine atoms of higher valency. Iodobenzene and other aromatic compounds with a nuclear iodine atom, can add on two atoms of chlorine; thus, for example, *phenyliodochloride*, $C_6H_5ICl_2$, is produced from iodobenzene.

By treating this compound with alkali, an *iodoso*-compound, e.g. *iodosobenzene* C_6H_5IO , is obtained. These are amorphous, yellow substances, which are converted into *iodoxy*-compounds by heating or by oxidation with bleaching powder:



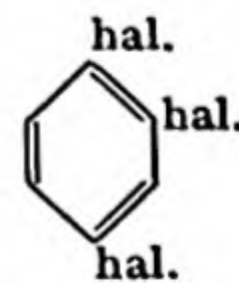
Iodoxybenzene may also be obtained by oxidising iodobenzene with perbenzoic acid; it is a crystalline compound which explodes on heating.

Iodosobenzene liberates iodine from acidified potassium iodide solution and is thereby converted into iodobenzene, from which it follows that the oxygen atom in iodosobenzene is attached to the iodine atom.

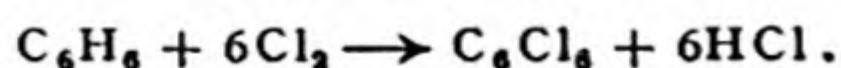
Di-halogeno-substitution products of benzene. *Para*- (1,4-) and *ortho*- (1,2-) dihalogenobenzenes are produced by chlorinating or brominating mono-halogenobenzenes at slightly elevated temperatures and in presence of ferric chloride or bromide as catalyst; *meta*- (1,3-) dihalogenobenzenes are produced only in very small quantities in this way.

The *para*-dihalogeno-compounds are solid, the *o*- and *m*-isomers are liquid. Pure *m*-dichloro- or *m*-dibromo-benzene are best prepared by reduction of *m*-chloro- or *m*-bromo-nitrobenzene to *m*-chloro- or *m*-bromo-aniline and replacement of the amino-group by halogen via the corresponding diazonium compound (245).

Tri-halogeno-compounds of benzene. When three halogen atoms are introduced into the nucleus, the main product formed is the asymmetric trihalogeno-benzene (1,2,4-), since this compound can be produced from all three (*o*-, *m*- and *p*-) dihalogeno-



Hexachlorobenzene ("JULIN's carbon chloride"), m.p. 229° , is produced by the continued chlorination of benzene until all six atoms of hydrogen are replaced eventually by chlorine:



221. Mono-halogeno-compounds of toluene. These comprise the *halogeno-toluenes* in which the halogen atom is introduced into the nucleus and the *benzyl halides*, in which the halogen atom is introduced into the side-chain.

Chloro- and bromo-toluenes are produced by allowing the appropriate halogen to react with toluene at ordinary or elevated temperatures or in sunlight in the presence of catalysts such as ferric or aluminium halides:



In this case a mixture of *ortho*- and *para*-halogeno-toluenes is the main product. These substances are also obtained when chlorine or bromine is dissolved in toluene at ordinary temperatures; when light is excluded a halogen atom is slowly introduced into the nucleus in the *o*- and *p*-positions to the methyl group.

When bromine is allowed to react with toluene at 50° in the dark in the absence of metal halides, substitution takes place in both the nucleus and the side-chain and besides bromotoluene, *benzyl bromide* (*phenylbromomethane*) $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$, is formed. The relative quantity of this compound is influenced by the concentration of the halogen in the reaction mixture. Increase in temperature and excess of toluene favour substitution in the side chain; at 100° benzyl halide is produced quantitatively.

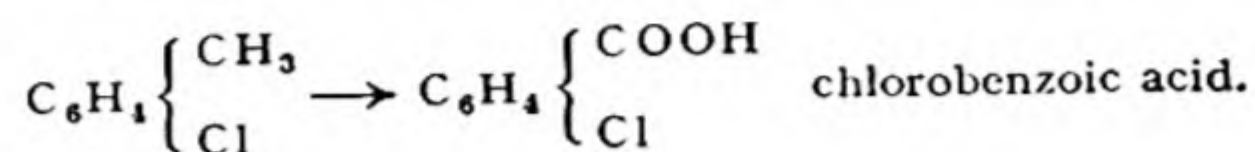
On irradiation, substitution takes place almost exclusively in the side chain even at room temperatures; this is the case only in the absence of iron or aluminium halide. If these catalysts are present, substitution takes place exclusively in the nucleus both on irradiation and at higher temperatures.

TABLE 42

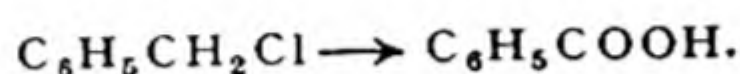
SOME PHYSICAL CONSTANTS OF MONO-HALOGENO-DERIVATIVES OF TOLUENE

Name	Formula	Boiling point °C	Melting point °C	Specific gravity d_4^{20}	Refractive index n_D^{20}
<i>o</i> -Chlorotoluene	$\text{C}_6\text{H}_4(\text{CH}_3)\text{Cl}$ 1 2	159.5	—36.2	1.0817	1.5238
<i>m</i> - „	$\text{C}_6\text{H}_4(\text{CH}_3)\text{Cl}$ 1 3	161.6	—47.8	1.0725	1.5214
<i>p</i> - „	$\text{C}_6\text{H}_4(\text{CH}_3)\text{Cl}$ 1 4	162	+ 6.2	1.0697	1.5199
<i>o</i> -Bromotoluene	$\text{C}_6\text{H}_4(\text{CH}_3) (1) \text{Br} (2)$	181.7	—25.9	1.4173 ₄ ²⁵	1.5460 ⁴⁰
<i>m</i> - „	$\text{C}_6\text{H}_4(\text{CH}_3) (1) \text{Br} (3)$	183.7	—39.8	1.4099	1.5448 ⁴⁰
<i>p</i> - „	$\text{C}_6\text{H}_4(\text{CH}_3) (1) \text{Br} (4)$	185.2	+26.6	1.3898	
Benzyl chloride	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	179.3	—39.0	1.1138 ₄ ¹⁵	1.5415 ¹⁵
Benzyl bromide	$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	198	— 3.9	1.4380 ₆ ²²	
Benzyl iodide	$\text{C}_6\text{H}_5\text{CH}_2\text{I}$	93/10 mm.	+24	1.7335 ₄ ⁵	

Properties of the halogenotoluenes. These substances have a faint, not unpleasant odour. Some of the physical constants for the three isomeric chloro- and bromotoluenes are given in Table 42. The halogen atom in these compounds is bound as firmly as in the halogenobenzenes. On oxidation they are converted into halogenobenzoic acids (261):



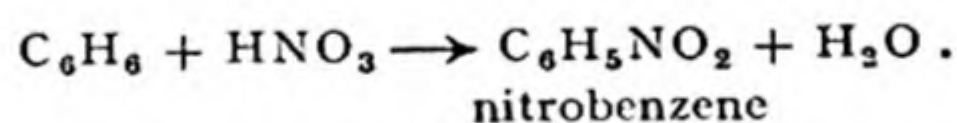
Properties of the benzyl halides. These are colourless liquids, which may be recognised by their powerful, irritating, lachrymatory odour. The halogen atom in benzyl halides is as readily reactive as that in alkyl halides (40). The benzyl halides give benzoic acid (260) on oxidation:



Di-halogeno-substitution products of toluene. Of these only the side-chain substituted compounds will be specially mentioned. Phenyldichloro- and phenyldibromo-methane (benzal chloride and bromide), $\text{C}_6\text{H}_5\text{CHCl}_2$ and $\text{C}_6\text{H}_5\text{CHBr}_2$, are produced by allowing chlorine or bromine to react with boiling toluene for a longer time. In this case, trisubstitution products such as $\text{C}_6\text{H}_5\text{CCl}_3$ (benzotrichloride) and $\text{C}_6\text{H}_5\text{CBr}_3$ are also obtained.

(iii) NITRO-COMPOUNDS OF BENZENE AND ITS HOMOLOGUES

222. *Mono-nitro-compounds* are obtained by allowing an excess of concentrated nitric acid or a mixture of concentrated nitric acid and concentrated sulphuric acid to react with benzene or one of its homologues:



During the nitration, water is produced, which dilutes the nitric acid. If nitric acid alone is used, an excess must be employed, since nitration no longer takes place once the water content reaches a certain value. When a mixture of strong nitric acid and strong sulphuric acid is employed, rather more than the theoretical amount of nitric acid suffices. In some cases fuming nitric acid ($d = 1.52$) is used.

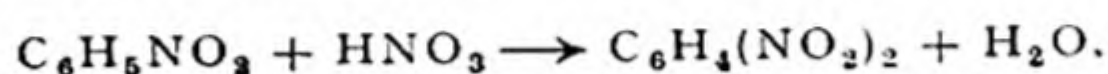
The nitration of aromatic hydrocarbons is an exothermic reaction; it is not reversible. When nitrobenzene is heated with water at 200° it remains unaltered.

Properties. None of the hydrogen atoms in aromatic nitro-compounds can be replaced by metals, as is the case with primary and secondary aliphatic nitro-compounds (50), because the nitro-group is here attached

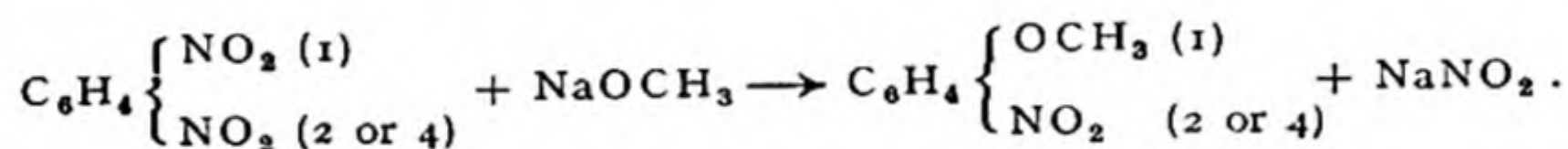
to a tertiary carbon atom, *i.e.* no hydrogen is present on the carbon atom carrying the nitro-group. The mono-nitro-compounds can be distilled without decomposition; the nitro-group is bound very firmly. Amines (236) are produced by the reduction of nitro-compounds.

Nitrobenzene is a pale yellow coloured liquid with an odour of bitter almonds; it is poisonous, especially in the form of vapour. Its physical constants are given in Table 43 on page 354. It is used in industry on a large scale as the starting product for the preparation of aniline (236).

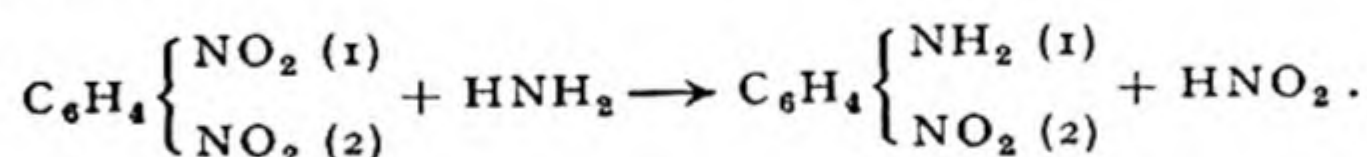
Dinitro-compounds of benzene are produced by nitrating nitrobenzene with a mixture of fuming nitric acid and concentrated sulphuric acid. The main product is *meta-dinitrobenzene* (m.p. 90°) with a little *ortho-dinitrobenzene* and a very small quantity of the *para*-isomer:



Properties. While the nitro-group is very firmly bound in mononitro-compounds, it is much less so in dinitro-compounds, if the nitro-groups are in the *ortho*- or *para*-positions to one another. Thus one of the nitro-groups in *o*- or *p*-dinitrobenzene can be replaced by OCH_3 or OC_2H_5 by the action of sodium methylate or ethylate:



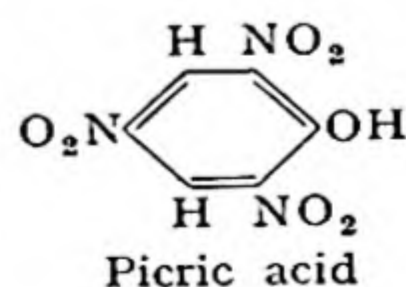
o-Nitraniline (240) is produced from *o*-dinitrobenzene by heating with alcoholic ammonia:



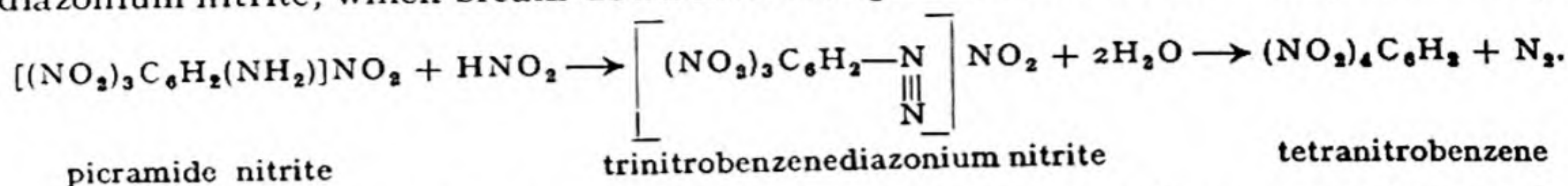
m-Dinitrobenzene is reduced to *m*-phenylenediamine (238) which is used in the preparation of dyestuffs; for this reason *m*-dinitrobenzene is also of great commercial importance.

223. *Trinitro-compounds of benzene.* Symmetrical trinitrobenzene-1,3,5, m.p. 121° , is produced by heating *m*-dinitrobenzene with a mixture of nitric acid and oleum to 140° . It is not possible to introduce more than three nitro-groups into benzene by direct nitration. It is remarkable that in symmetrical trinitrobenzene, in which all the nitro-groups are situated in the *meta* position to one another, one of the groups is very readily replaced by OCH_3 , yet this is not the case in *m*-dinitrobenzene.

The polynitrobenzenes can be oxidised. With *m*-dinitrobenzene the oxidation proceeds incompletely to 2,6-dinitrophenol, but trinitrobenzene can be easily oxidised to trinitrophenol or picric acid (235).



1,3,4,5-Tetranitrobenzene is obtained by the action of NO and NO₂ on a solution of 1,3,5-trinitro-4-aminobenzene (*picramide*, 225) in strong nitric acid. It must be supposed that the picramide is diazotised (245) with the formation of trinitrobenzene-diazonium nitrite, which breaks down into nitrogen and *tetranitrobenzene* (HOLLEMAN):



Tetranitrobenzene melts at 130°. This substance can be made to explode violently by means of a priming explosive.

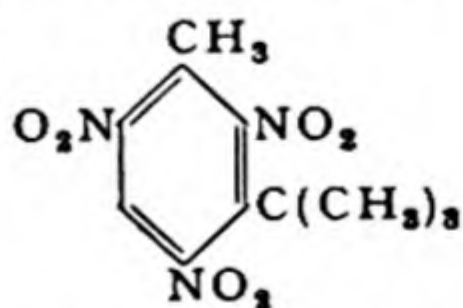
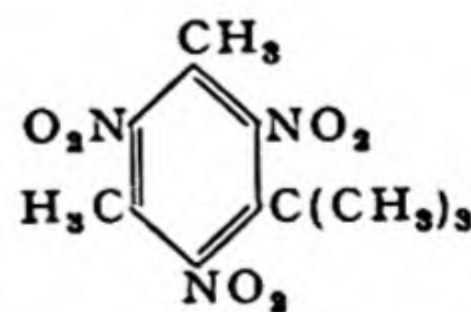
Nitrotoluene. The nitration of toluene with a mixture of concentrated nitric acid and sulphuric acid takes place more readily than the nitration of benzene; the velocity of nitration is increased by the presence of an alkyl group in the benzene nucleus. At 0°, 58.8 % of *ortho*-, 36.8 % of *para*- and 4.4 % of *meta*-nitrotoluene are produced. In other cases, where the *o*- and the *p*-isomers are formed together, as a rule, more of the *p*- than of the *o*-compound is produced.

TABLE 43

SOME PHYSICAL CONSTANTS OF NITROBENZENE AND THE NITROTOLUENES

Name	Formula	B.p. °C	M.p. °C	Spec. grav. d ₄ ²⁰	Refractive index n _D ²⁰
Nitrobenzene	C ₆ H ₅ NO ₂	209.2	+ 5.70	1.2032	1.5530
<i>o</i> -Nitrotoluene	C ₆ H ₄ (CH ₃)NO ₂	220	— 3.2	1.1622	1.5463
<i>m</i> -Nitrotoluene	C ₆ H ₄ (CH ₃)NO ₂	232.6	+16	1.1600	1.5470
<i>p</i> -Nitrotoluene	C ₆ H ₄ (CH ₃)NO ₂	237.7	+51.6	1.0817 d ₄ ¹⁰⁰	
<i>o</i> -Dinitrobenzene	C ₆ H ₄ (NO ₂)NO ₂	319	117	1.3119 d ₄ ¹²⁰	
<i>m</i> -Dinitrobenzene	C ₆ H ₄ (NO ₂)NO ₂	302	89.8	1.3349 d ₄ ¹²⁰	
<i>p</i> -Dinitrobenzene	C ₆ H ₄ (NO ₂)NO ₂	299	172		

Polynitro-compounds of toluene and xylene. On further nitration of toluene, 2,4,6-trinitrotoluene is produced; this substance is known technically under the name of *trotyl*, and is used on a large scale as an explosive.

Trinitro-*tert.*-butyltoluenetrinitro-*ter.*-butyl-*m*-xylene

possess a very intense odour of musk; the former compound is used in perfumery as *artificial musk*.

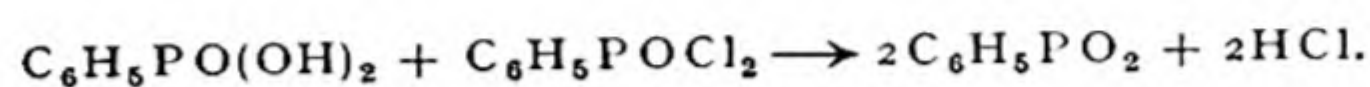
Natural musk is derived from the male musk-deer and contains *muscone* (293) to

which it owes its odour. This compound has not the slightest similarity in composition to artificial musk. *Musk-ambrette*, $\text{C}_6\text{H}(\text{CH}_3)_1(\text{OCH}_3)_5[\text{C}(\text{CH}_3)_2]_2(\text{NO}_2)_{4,6}$, m.p. 85° , also has a musk-like odour.

The mono- and di-nitrotoluenes are of importance technically as the starting materials for the preparation of the corresponding amines.

Aromatic compounds containing phosphorus and arsenic, analogous to nitro-compounds in composition, are also known.

Phosphobenzene, $\text{C}_6\text{H}_5\text{PO}_2$, cannot be obtained by the action of metaphosphoric acid on benzene. It is produced by allowing *phenylphosphonic acid* to react with its chloride:

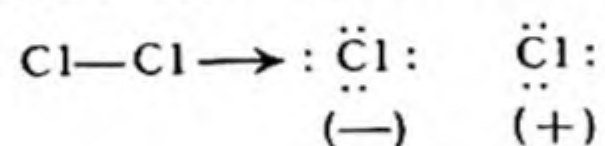


Arsobenzene $\text{C}_6\text{H}_5\text{AsO}_2$, (phenylarsonic anhydride) is produced by heating phenylarsonic acid, when a molecule of water is split off.

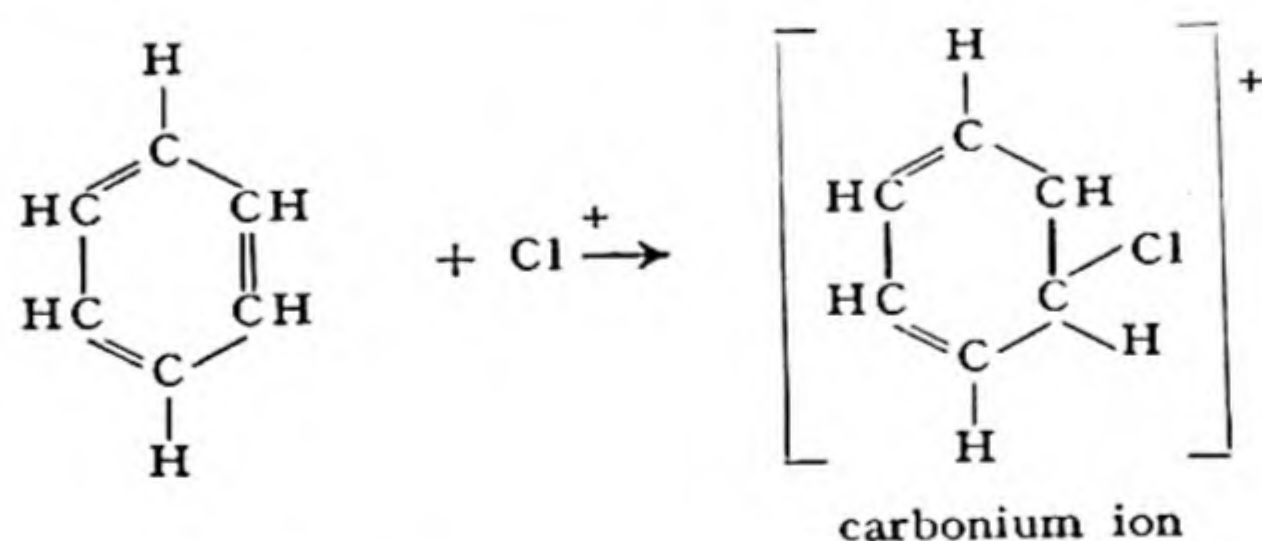
224. The mechanism of aromatic substitution.

The course of the substitution of a hydrogen atom by a halogen atom can be represented as follows:

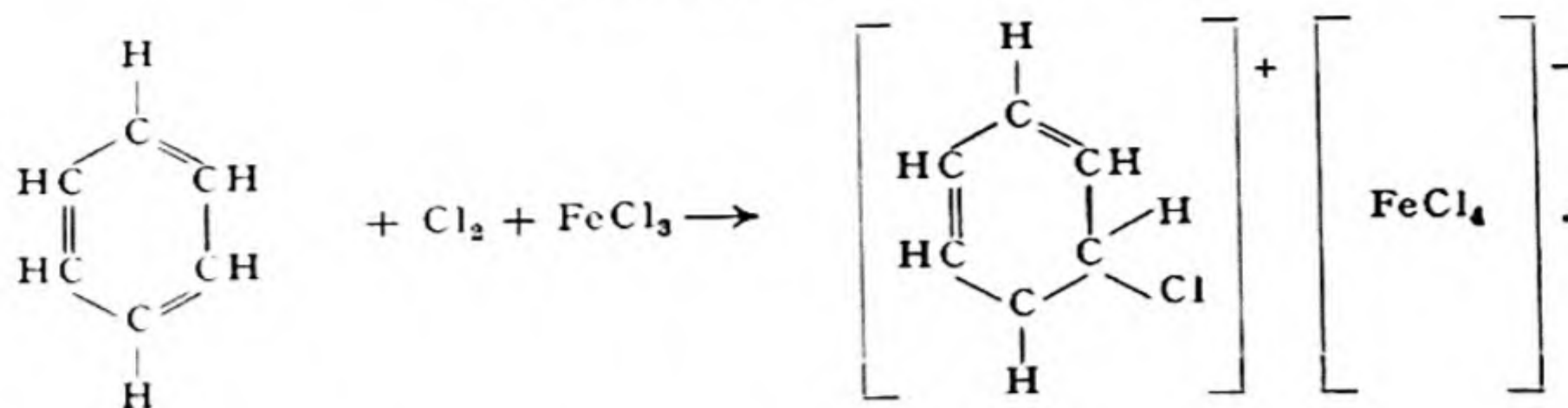
1st The halogen molecule is polarised, *i.e.* one of the halogen atoms acquires a positive charge and the other a negative charge:



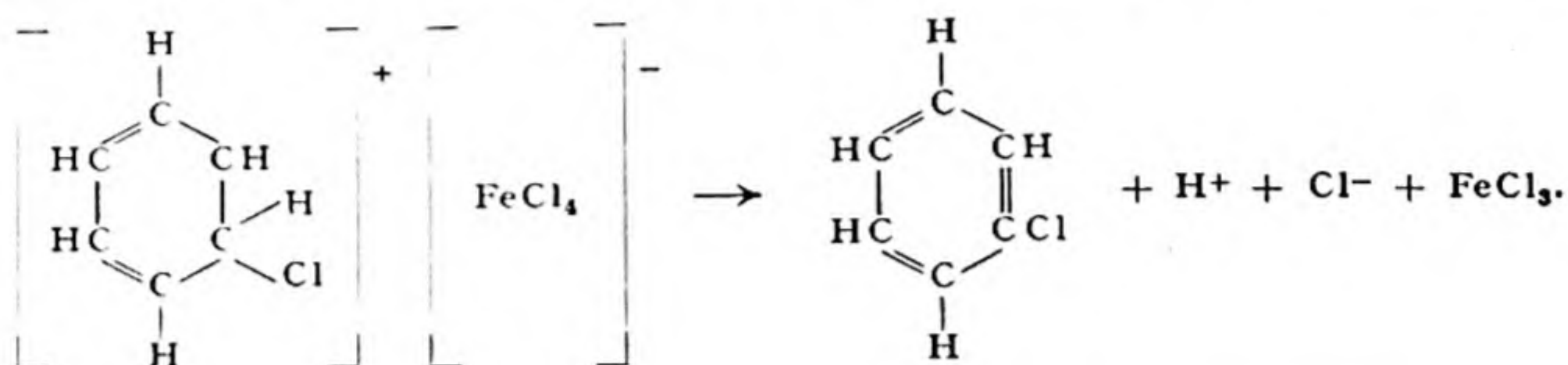
2nd The positively charged halogen atom forms a covalent bond with a carbon atom in the benzene ring; for this to happen it is necessary for this carbon atom to have a free pair of electrons for disposal. This comes about by the polarisation of the benzene ring under the influence of the positive halogen particle, whereby two π -electrons become available from the reacting carbon atom. By this means a positively charged *carbonium ion* is produced:



The fission of the halogen molecule into positive and negative ions is facilitated by the presence of metal chlorides such as FeCl_3 , AlCl_3 and SbCl_5 , since these substances readily form complex compounds; a negative complex ion $[\text{FeCl}_4]^-$ may be produced from a negatively charged chlorine ion Cl^- and FeCl_3 . The first step in the substitution may therefore be represented as follows:

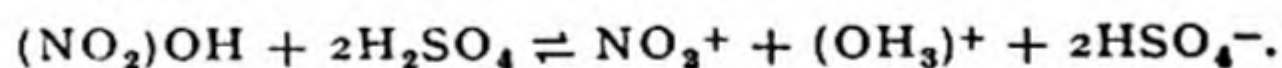


The carbonium ion then loses a proton and the complex salt breaks down:



According to this theory the catalytic action of the above mentioned chlorides in halogenations, is connected with the tendency of these substances to form complexes (PFEIFFER and WIZINGER; PRICE). The hydrogen atom to be substituted is repelled as a cation (proton); it must therefore be replaced by another cation. Thus in this case an entering positive halogen ion finds a carbon atom on which the pair of electrons necessary to form the bond is already present. This type of substitution is known as *electrophilic substitution* (INGOLD) or *cationoid substitution* (ROBINSON).

In nitration we have another example of electrophilic substitution. Nitrating acid (a mixture of nitric acid and sulphuric acid) shows neither the ultra-violet spectrum of the NO_3 ion nor that of the HNO_3 molecule. The very low vapour pressure of a solution of nitric acid in anhydrous sulphuric acid shows that in such a solution the nitric acid is not present as such. In the Raman spectrum there occurs a frequency of 1400^{-1} cm., which is ascribed to the *nitronium ion*, NO_2^+ . From measurements on the lowering of the freezing point, it appears that in solutions of nitric acid in sulphuric acid, four new species of molecules are produced from each molecule of nitric acid, thus:

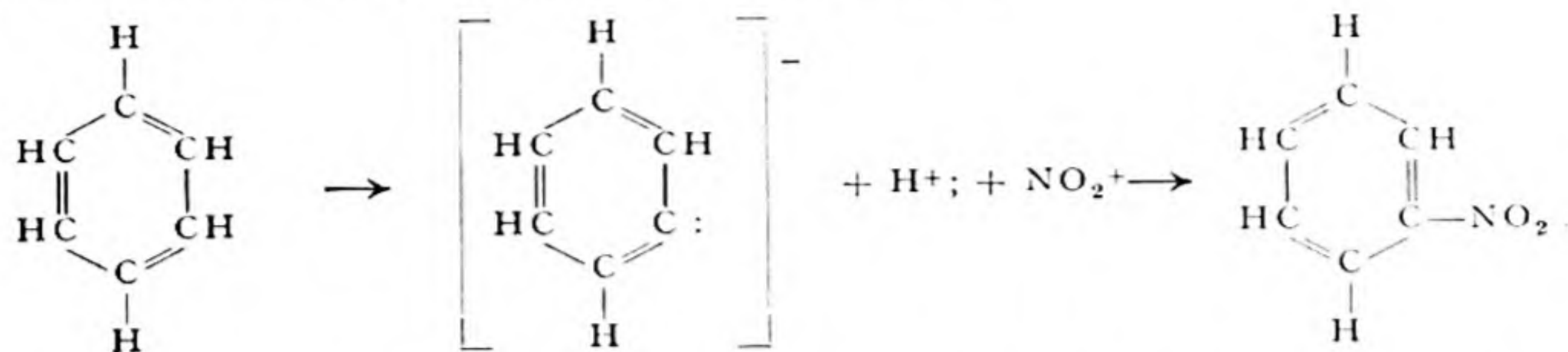


When nitrating acid is electrolysed, the concentration of nitric acid increases at the cathode, which indicates that the NO_2^+ ion (which is determined as nitric acid in the analysis) migrates towards the cathode.

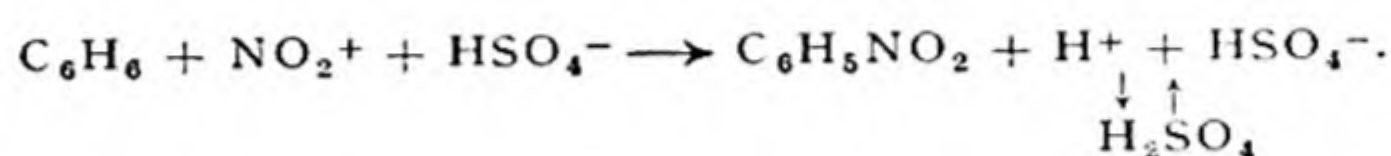
According to the equation given above, the formation of NO_2^+ is reversible and is favoured by an excess of sulphuric acid.

A mixture of acids containing a certain quantity of water cannot bring

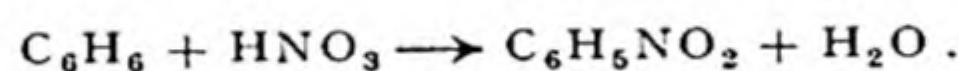
about the nitration of benzene; such a mixture fails to show the Raman frequency of the nitronium ion. It may be concluded therefore that the nitronium ion is the principal nitrating agent:



The benzene molecule repels a proton and is thereby converted into a negative ion, which combines with NO_2^+ . An HSO_4^- -ion which is present, serves as a proton acceptor with the formation of sulphuric acid:



According to the empirical equation for nitration, water is split off in the process:



In nitration with a mixture of sulphuric and nitric acids, this splitting off of water occurs before the molecule, to be nitrated, enters into reaction.

It should be mentioned, that not every nitration of an aromatic compound takes place according to this scheme. Phenol, for example, is nitrated even by dilute nitric acid, in which no NO_2^+ -ions are present; in this case, it is assumed that the nitric acid molecules act as the nitrating agent.

225. Halogeno-nitro-compounds of benzene. Nitration of chlorobenzene at ordinary temperatures affords 70 % of *para*- and 30 % of *ortho*-nitrochlorobenzene $\text{C}_6\text{H}_4 \begin{cases} \text{NO}_2 & (1) \\ \text{Cl} & (4,2) \end{cases}$. A mixture of *o*- and *p*-nitrohalogenobenzenes, in which the *para*-compound predominates, is also obtained on nitrating fluoro-, bromo- or iodo-benzene. On the other hand, *m*-chloro- and *m*-bromonitrobenzene are the main products obtained in the chlorination and bromination of nitrobenzene. This may be carried out by passing chlorine, for example, into a mixture of nitrobenzene and antimony chloride at an elevated temperature, the antimony chloride acting as a chlorine carrier.

Properties. The halogen atom in *o*- and *p*-halogenonitrobenzenes is quite reactive; it is replaced by OCH_3 or by NH_2 by heating with an alcoholic solution of sodium methylate or ammonia, respectively. The halogen atom in *m*-halogenonitrobenzenes is as unreactive as that in the mono-halogenobenzenes (220).

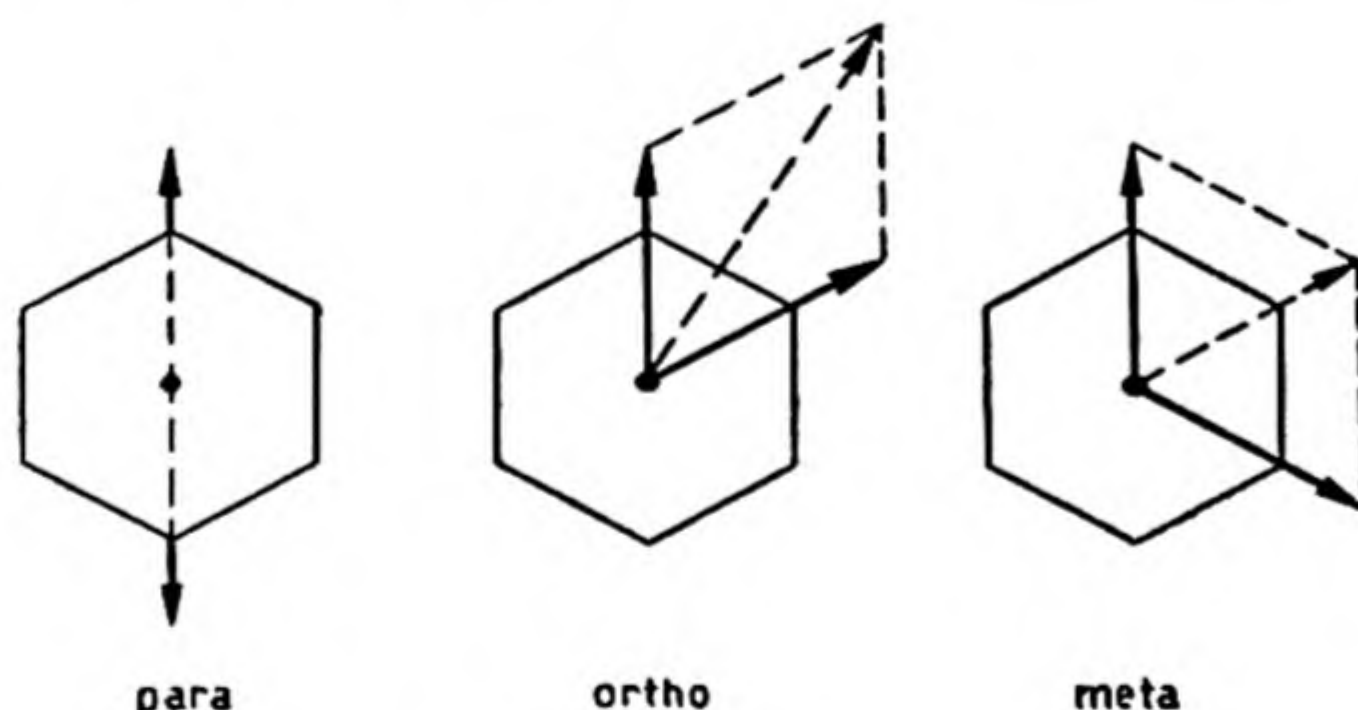
The reactivity of the halogen atom is still greater in those halogenonitrobenzenes in which there are two or three nitro-groups in *o*- and *p*-positions to the halogen atom, *e.g.* in 1-chloro-2,4,6-trinitrobenzene or *picryl chloride*, $\text{C}_6\text{H}_2\text{Cl}(\text{NO}_2)_3$. The halogen atom in this compound can be displaced very easily. This substance behaves like the chloride of a carboxylic acid; with hot water it is decomposed into hydrochloric acid and *picric acid*, $\text{C}_6\text{H}_2(\text{NO}_2)_3\text{OH}$ (235), while with ammonia it gives *picramide*, $\text{C}_6\text{H}_2(\text{NO}_2)_3\text{NH}_2$.

It is seen from these examples, that the reactivity of atoms or groups of atoms substituted in the benzene nucleus, can be very strongly influenced by other groups in the benzene ring, both the character of these groups and the position they occupy with respect to one another having an effect (see 272).

The nitro-groups in the halogenonitrobenzenes can be replaced by chlorine by heating with thionyl chloride, SOCl_2 .

Measurement of the dipole moments of disubstitution products of benzene has led to results of considerable interest. Chlorobenzene has a dipole moment of $\mu = -1.55 \times 10^{-18}$; this may be considered as the moment of the dipole between the phenyl residue and the chlorine atom. Since this atom is negatively charged with respect to the phenyl residue, the negative pole of the dipole is diverted from the phenyl residue. This is indicated by giving the dipole moment a negative sign.

When two chlorine atoms are substituted in the benzene molecule, the simplest assumption is, that the total dipole moment can be calculated by vector-addition of the dipole moments of the chlorine atoms.



From the above figures it follows, that for the *para*-isomer the total moment $= \mu - \mu = 0$.

$$\text{„ „ } \textit{ortho-} \text{ „ „ „ „ } = \sqrt{\mu^2 + \mu^2 + 2\mu^2 \cos 60^\circ} = \mu \sqrt{3}.$$

$$\text{„ „ } \textit{meta-} \text{ „ „ „ „ } = \sqrt{\mu^2 + \mu^2 + 2\mu^2 \cos 120^\circ} = \mu.$$

In these formulae μ is the dipole moment of chlorobenzene. In the same way dipole moments may be calculated of molecules of disubstituted derivatives of benzene with dissimilar substituents, in which case the sign (+ or —) must be taken into account. In this case the *para*-compound has a final moment.

Some experimentally found and calculated values for various substitution products of benzene are collected in Table 44.

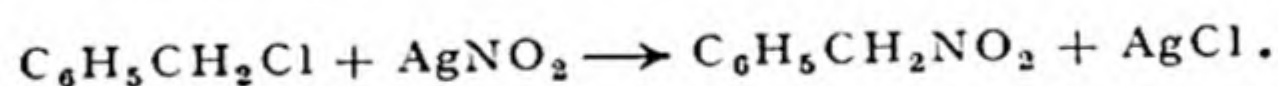
TABLE 44
DIPOLE MOMENTS OF SOME BENZENE DERIVATIVES

	Dipole moments $\times 10^{18}$	
	observed	calculated
1,2-Dichlorobenzene	—2.27	—2.7
1,3- "	—1.52	—1.6
1,4- "	0	0
Nitrobenzene	—3.8	
1,2-Dinitrobenzene	—6.02	—6.5
1,3- "	—3.75	—3.80
1,4- "	—0.3	0
1-Nitro-2-chlorobenzene	about —4	—4.8
1-Nitro-3-chlorobenzene	—3.3	—3.3
1-Nitro-4-chlorobenzene	—2.45	—2.2

The agreement between observation and calculation is satisfactory, in general, for *meta*- and *para*-derivatives, and this may be considered as confirming the hexagonal formula for benzene derived from chemical data. With *ortho*-derivatives the deviations are greater than the errors of observation; these deviations indicate an interaction between two neighbouring substituents.

Nitro-compounds with the nitro-group in the side-chain.

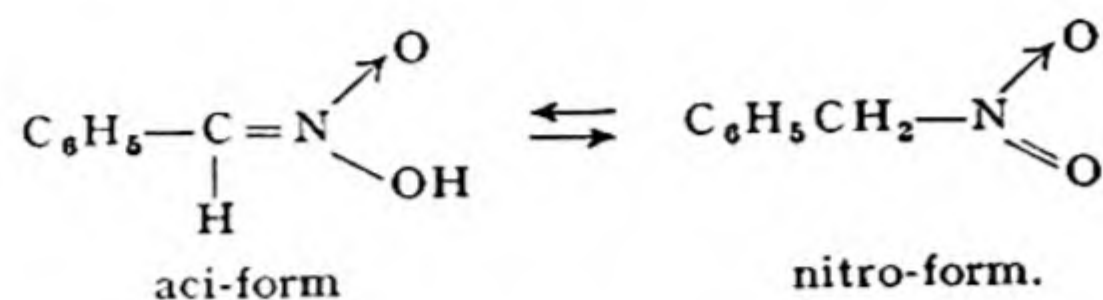
226. *Phenylnitromethane*, $C_6H_5CH_2NO_2$, is prepared by the action of silver nitrite on benzyl chloride or iodide:



On reduction it forms benzylamine (239), which can also be obtained from benzyl chloride and ammonia; from this it follows that the nitrogen atom in phenylnitromethane is attached to the carbon atom in the side-chain.

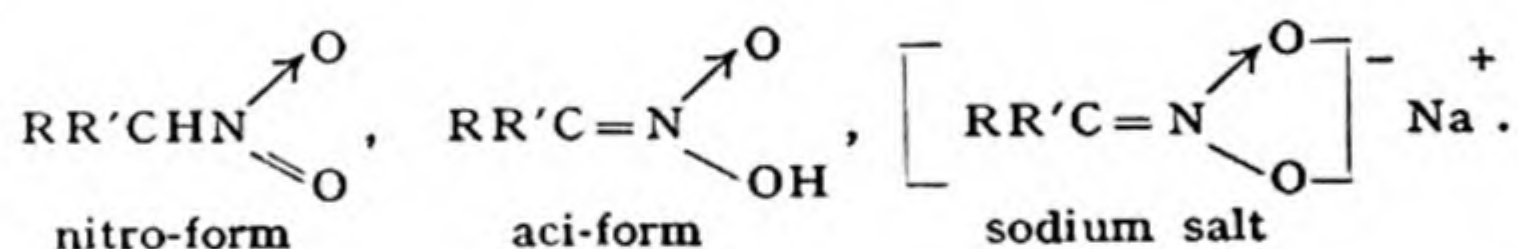
Properties. Phenylnitromethane is one of the oldest known examples of a compound which can exist in two tautomeric forms (HOLLEMAN; HANTZSCH 1896); the stable form is liquid and gives no coloration with an aqueous solution of ferric chloride. Like nitromethane, (50), phenylnitromethane gives a sodium derivative having the composition $C_6H_5CHNa(NO_2)$, with sodium alcoholate. When an equivalent quantity of mineral acid is added to an aqueous solution of this sodium derivative, a crystalline modification of phenylnitromethane separates; this form gives a colour reaction with an aqueous solution of ferric chloride. At ordinary temperature the crystalline form passes slowly into the liquid form and is therefore metastable. At low temperatures the metastable form reacts violently with *phenyl isocyanate*,

C_6H_5NCO (compare 155), which points to the presence of a hydroxyl group. Therefore since it also gives a sodium derivative, and has acid properties, the structure given below, designated as the *aci-form*, is attributed to this modification:



The conversion of the aci-form into the nitro-form has been more closely studied with *m*-nitrophenylnitromethane, $C_6H_4 \begin{cases} CH_2NO_2 & (1) \\ NO_2 & (3) \end{cases}$. The stable form of this compound is colourless, while the sodium salt is coloured deep yellow. When an equivalent of hydrochloric acid is added to an aqueous solution of the sodium derivative, the yellow colour slowly disappears and at the same time the electrical conductivity of the liquid decreases. From this it follows that the aci-form, which shows conductivity in aqueous solution, is responsible for the yellow colour of the solution and that the stable nitro-form has no acid properties.

By analogy with the above, it is assumed that the alkali compounds of primary and secondary aliphatic nitro-compounds (50) are derived from an aci-form:



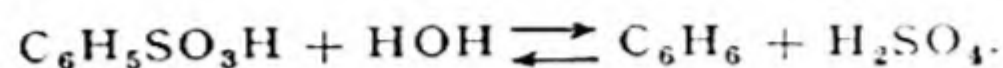
Substances, which are first converted into aci-forms in the formation of metal compounds, are called *pseudo-acids* (compare 235 and 275).

(iv) SULPHONIC ACIDS OF BENZENE AND ITS HOMOLOGUES

227. *Mono-sulphonic acids* of benzene and its homologues are produced by the action of concentrated sulphuric acid or weak fuming sulphuric acid on aromatic hydrocarbons.

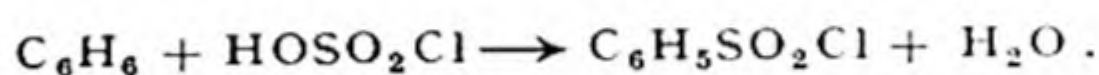
If this reaction is carried out at ordinary temperature, a large excess of sulphuric acid is necessary since it is diluted by the water formed in the reaction; a concentration of more than 65 % sulphuric acid is necessary for sulphonation to take place. However, if benzene vapour is passed through sulphuric acid heated to 170–180°, the water formed is evaporated off from the reaction mixture so that practically the whole of the sulphuric acid can be converted into benzenesulphonic acid. The barium and calcium salts of benzenesulphonic acid are readily soluble in water, so that aromatic sulphonic acids can be separated from sulphuric acid by means of these salts (cf. ethylsulphuric acid 40).

Properties. The sulphonic acids are colourless, crystalline compounds, which are readily soluble in water and frequently hygroscopic. They are split up into sulphuric acid and the corresponding aromatic hydrocarbons by heating with water under pressure. Hence sulphonation is a reversible process:



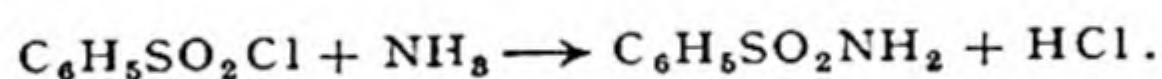
Use is made of this reaction to separate aromatic hydrocarbons from mixtures with alkanes; the former are converted by warming with concentrated sulphuric acid into sulphonic acids, which are soluble in water, while the alkanes remain unaltered.

The salts of the sulphonic acids usually crystallise well and are used in order to obtain the acids in a state of purity. On treating the alkali salts with phosphorus pentachloride they are converted into *sulphonyl chlorides*, which are also produced directly by the action of chlorosulphonic acid on aromatic hydrocarbons. Benzenesulphonyl chloride, m.p. 14.5° , is produced from benzene:



The *sulphonyl chlorides* have a very unpleasant smell. They are only slowly converted into sulphonic acids by cold water.

Sulphonamides are produced from the chlorides by treating them with concentrated aqueous ammonia:



They are well-defined crystalline compounds, which may be used for identifying aromatic hydrocarbons. On account of the acid character of the $\text{C}_6\text{H}_5\text{SO}_2$ -group, the hydrogen atoms in the NH_2 -group are replaceable by metals. The sulphonamides are soluble in alkalis and ammonia.

Reduction of sulphonic acids produces *thiophenols*, e.g. $\text{C}_6\text{H}_5\text{SH}$, which can be reconverted into sulphonic acids by oxidation (with nitric acid). The sulphonyl group $-\text{SO}_2\text{H}$, can be replaced by cyano- and hydroxyl groups (260, 229).

Toluenesulphonic acids. On sulphonating toluene, *o*- and *p*-toluenesulphonic acids are produced as the main reaction products with only a few percent. of the *m*-isomer. When dissolved in an excess of sulphuric acid and warmed to 100° , the *o*- and *p*-compounds are slowly converted one into the other. This is another example showing that the sulphonyl group is not very firmly attached to the benzene nucleus.

Substituted benzenesulphonic acids. When chloro- or bromo-benzene is treated with oleum, practically the sole product is the *p*-halogenobenzene sulphonic acid, which has similar properties to benzenesulphonic acid. The

main product from the sulphonation of nitrobenzene is *m*-nitrobenzenesulphonic acid. This compound is produced also as the main product along with small amounts of the *ortho*- and *para*-compounds, by nitrating benzenesulphonic acid.

Disulphonic acids. On sulphonating benzene or its homologues with fuming sulphuric acid at 200–245°, the main product is the *m*-disulphonic acid. On heating with sulphuric acid for a long time at 209°, it is converted into the *p*-disulphonic acid, which itself can be converted partially into the *m*-isomer under the same conditions. The *o*-isomer is not formed in this way.

Trisulphonic acids of benzene and its homologues are produced along with the disulphonic acids. The formation of trisulphonic acids is facilitated by the addition of silver sulphate. No one has yet succeeded in introducing more than three sulpho-groups into the benzene nucleus by direct sulphonation.

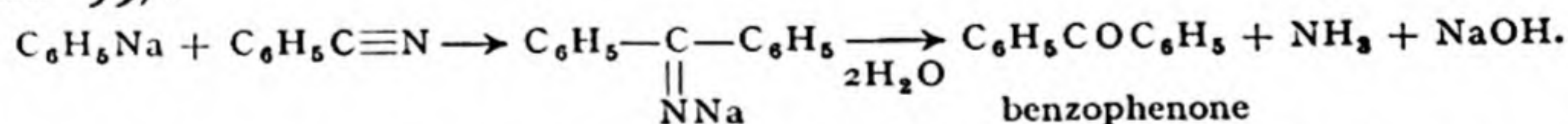
(v) SUBSTITUTION OF A GROUP CONTAINING MERCURY IN THE BENZENE NUCLEUS

When benzene is heated to 110° with mercuric acetate, *phenylmercuri-acetate*, $C_6H_5-HgOCOCH_3$, the acetate of the base C_6H_5HgOH , phenylmercuri-hydroxide, is formed. Homologues of benzene and their derivatives, *e.g.* nitrobenzene, give similar compounds (DIMROTH). *Ortho*-nitrophenylmercuri-acetate is the main product from nitrobenzene and mercuric acetate. On treatment with a solution of sodium chloride, phenylmercuri-acetate is converted into phenylmercuri-chloride, C_6H_5HgCl , which is insoluble in water. When this substance is shaken with bromine, bromobenzene is formed along with mercuric chloride and bromide.

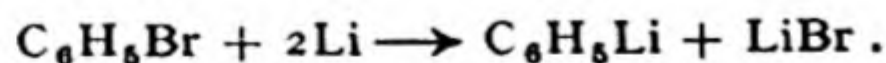
(vi) PHENYLMETAL COMPOUNDS

228. *Phenylsodium* is formed by the action of sodium on chlorobenzene in an inert solvent at about 40° and in an atmosphere of nitrogen.

When a stream of carbon dioxide is passed into a solution of phenylsodium, sodiumbenzoate is produced. By the action of phenylsodium on benzonitrile, the sodium derivative of a *ketimide* is produced from which benzophenone (259) is formed on hydrolysis (cf. the similar reaction with alkylmagnesium halides 59):



Phenyllithium is obtained by the action of lithium on an ethereal solution of bromobenzene:



Phenyllithium can be used for various syntheses.

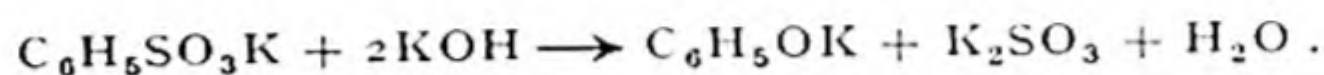
Diphenylmercury $(C_6H_5)_2Hg$, a stable, crystalline compound, is produced by the action of sodium amalgam on bromobenzene.

(vii) PHENOLS AND THEIR DERIVATIVES

(a) *Mono- and poly-hydric phenols*

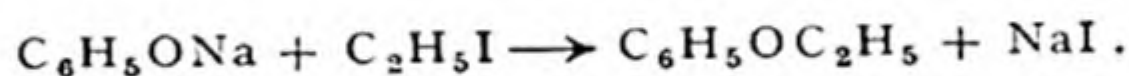
229. Phenols are compounds derived from aromatic hydrocarbons by replacing one or more nuclear hydrogen atoms by hydroxyl groups; they are usually discussed under the headings of mono-, di- and poly-hydric phenols.

Monohydric phenols. The alkali compounds of phenol and its homologues are produced by fusing a salt of a sulphonic acid with alkali:

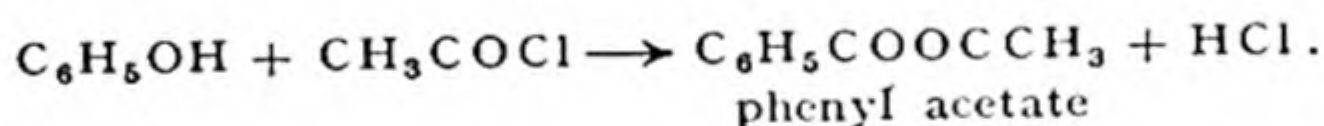


Phenols are also produced by the action of nitrous acid on primary aromatic amines (236). This method of formation is similar to that of alkanols from primary aliphatic amines (48), whereby the alkanols are produced directly. In the formation of phenols important intermediate products, namely the *diazonium compounds* (245), can be isolated.

Properties. The alcohol function of the alkanols is again found in the phenols. They can form ethers, for example, by allowing an alkyl halide to react with the sodium derivative of the phenol:



They form esters; an acetate is produced with acetyl chloride:



On treatment with phosphorus pentachloride the hydroxyl group is replaced by chlorine; this reaction takes place less readily than in the aliphatic series. In the vapour phase at about 770° , phenol is reduced by hydrogen to benzene.

Phenols cannot be oxidised to aldehydes or ketones with the same number of carbon atoms, since the carbon atom to which the hydroxyl group is attached carries no hydrogen atoms. In this respect the phenols are comparable with tertiary alcohols.

Phenols have a weakly acid character; aqueous solutions show a very small electrical conductivity. They easily form *phenolates* with alkalis. Aliphatic alcohols do not possess this property to the same degree; they give alcoholates only on treatment with alkali metals. The weakly acid properties of the phenols must be attributed to the effect of the phenyl group. This is expressed by saying that *phenyl has a stronger negative character than alkyl*. Phenolates may be regarded as salts of very weak acids, they are decomposed by carbonic acid. If the structural formula of KEKULÉ is ascribed

to benzene, the hydroxyl group in phenols is attached to a carbon atom carrying a double bond. It has been seen in 149 that the enol forms of ethyl acetate and acetylacetone are soluble in aqueous alkali with the formation of an enolate. Hence in this case also a hydroxyl group attached to a doubly bound carbon atom has weakly acid properties.

In aqueous solution phenols give a violet coloration with ferric chloride due to the formation of complex ferric compounds. This reaction has already been noted also with the enol-forms of esters of 2-keto-acids and 1,3-diones.

In phenol the hydrogen atoms in the nucleus can be much more easily substituted than in benzene. In aqueous solution, phenol gives directly a precipitate of *tribromophenol* with bromine water. This reaction is used for the quantitative determination of phenol. Phenol is easily converted into *nitrophenol* by treatment with dilute nitric acid, while concentrated nitric acid is necessary for the nitration of benzene. Phenols are also much more easily oxidised than aromatic hydrocarbons. The marked effect of the hydroxyl group on the reactivity of hydrogen atoms in the benzene nucleus is clearly apparent from these examples.

Phenol was isolated by RUNGE in 1834 from coal-tar and called *carbolic acid* (derived from carbo = coal and oleum = oil). Phenol crystallises in colourless needles, melts at 40.8° and boils at 181° . It has a characteristic odour and possesses powerful antiseptic properties; it is used as a disinfectant. It is soluble in water (15 parts at 16°), and conversely, water is slightly soluble in molten phenol; on account of the low molecular weight and the high molecular freezing point depression of phenol, viz. 75, a mixture of phenol with 5–6 % of water is liquid even at room temperature.

Phenol occurs with some of its homologues (cresols) in coal-tar; when the latter is fractionally distilled, they pass over in the carbolic and creosote oil, from which they are separated by extracting the appropriate fractions with caustic alkali; the phenols pass into solution and are recovered by passing in carbon dioxide. Finally, pure phenol is obtained by fractional distillation.

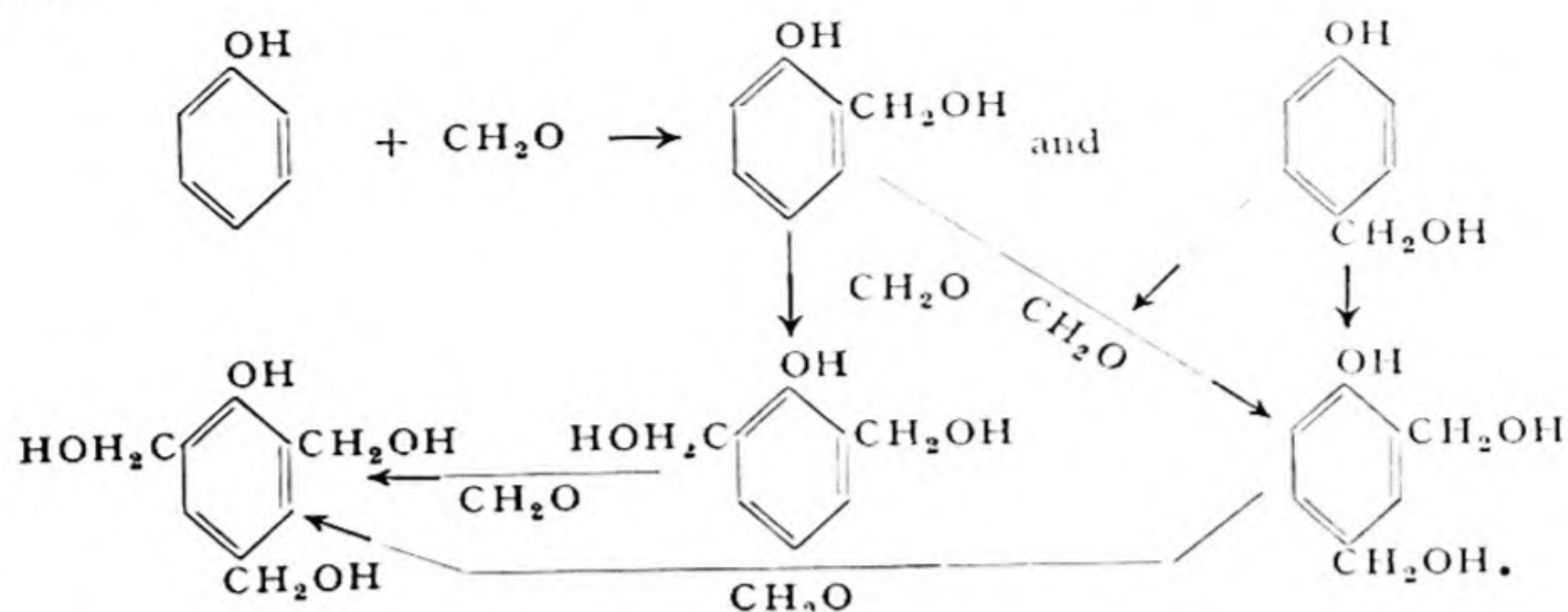
It is also prepared synthetically on a large scale for the chemical industry. In the earliest process, the starting material was the sodium salt of benzenesulphonic acid, which is converted by fusion with caustic soda into *sodium phenolate*, from which phenol is obtained by treatment with carbon dioxide.

According to a more recent method, which is widely used, the starting material is chlorobenzene, which is heated under a pressure of about 300 atm. to $370\text{--}380^{\circ}$, with dilute alkali to which copper salts have been added as catalysts. In this process, diphenyl ether (231) is produced as a by-product.

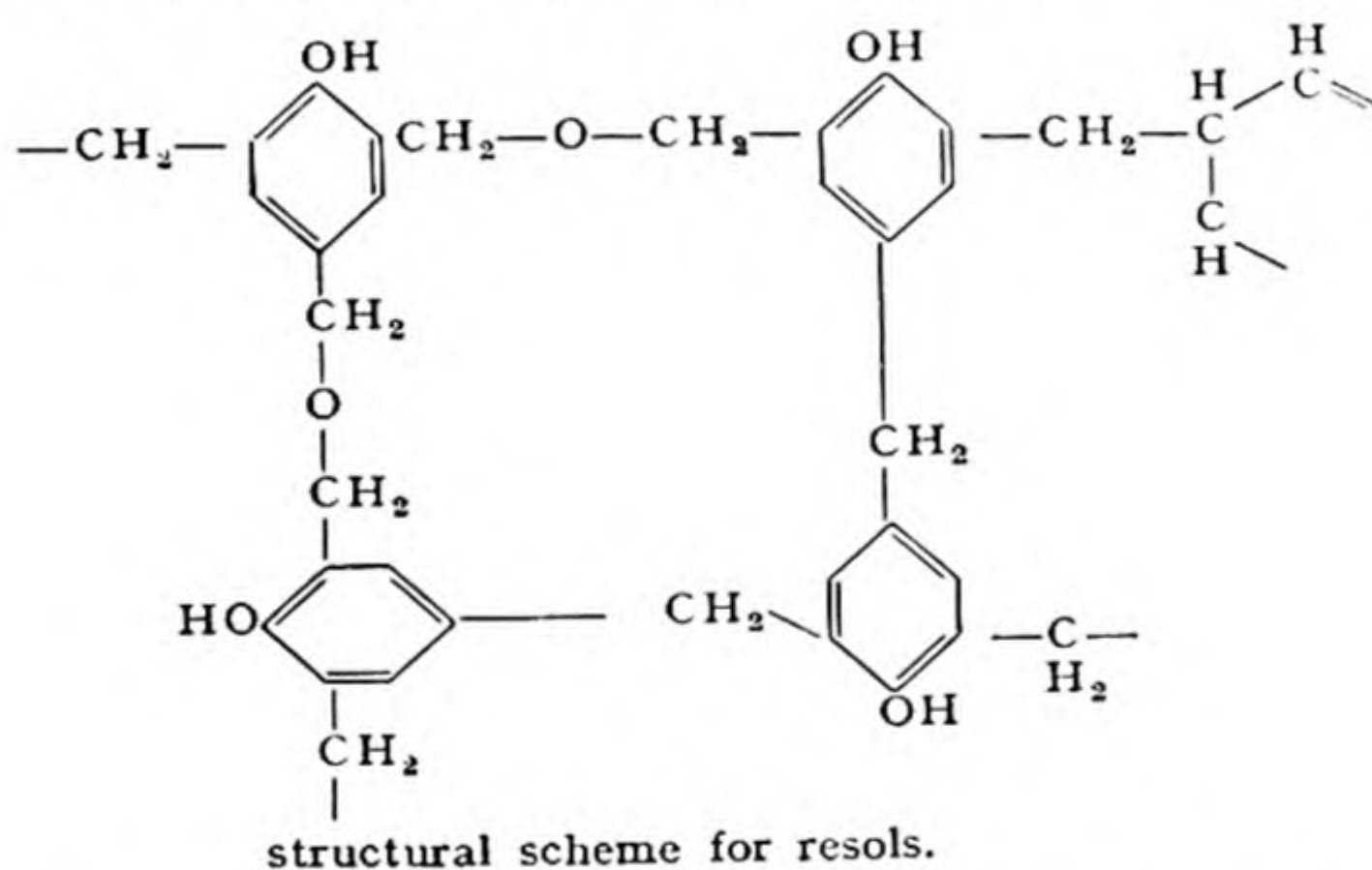
Phenol is used, for example, for the preparation of salicylic acid (263), picric acid, (235), various dyestuffs and artificial or synthetic resins.

By heating phenol with formalin (62) in weakly alkaline media, amorphous condensation products of high molecular weight are produced, which form the basis of synthetic resins and are known under the collective name of *phenoplasts* (BAEKELAND).

The initial products in this process are phenol-alcohols formed by addition of formaldehyde and phenol, the hydrogen atoms in the *o*- and *p*-positions taking part in the reaction:



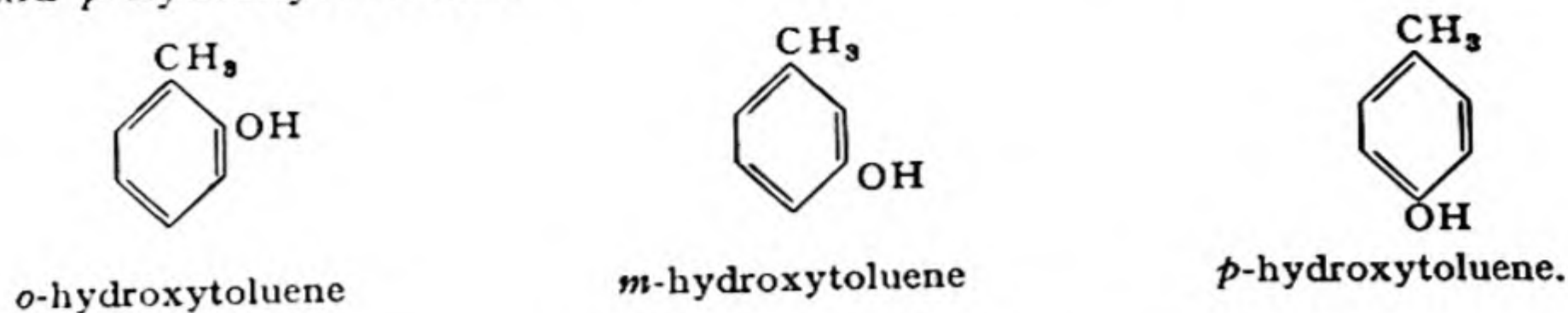
These phenol-alcohols undergo condensation reactions by which water is eliminated either between the CH_2OH -group and a hydrogen atom in an *o*- or *p*-position in the benzene nucleus, so that two benzene rings are connected by a CH_2 -group, or by ether formation between two CH_2OH -groups, with the formation of an ether bridge:



Thus in this way there are produced by *poly-condensation*, macromolecules having a highly branched, net-like structure. The formation of a net-work structure depends on the presence in each molecule of phenol-alcohol of three groups, which can undergo a condensation reaction, viz. the CH_2OH -groups and/or the hydrogen atoms in the *o*- or *p*-positions. This should be compared with the formation of linear macromolecules by polymerisation of ethene derivatives discussed in 103, where branching is not possible, since only two reactive positions occur in molecules represented by $\text{XCH}=\text{CHY}$ namely, at the doubly bound carbon atoms.

The artificial resins (resols) just described are fusible and soluble in organic solvents. They are used for the manufacture of moulding powders. On heating, these resols are converted into a hard infusible material (*resite*). Chemical changes take place in this process, e.g. formaldehyde is split off whereby ether bridges $-\text{CH}_2-\text{O}-\text{CH}_2-$ are converted into $-\text{CH}_2-$. The working of resols in hot presses, by which the initially thick, liquid material is converted during pressing to a hard infusible product, is based on these changes.

230. *Hydroxytoluenes* $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$, are called *cresols*, there being three isomers, *o*-, *m*- and *p*-hydroxytoluenes:



The mixture of isomeric cresols isolated from coal-tar consists mainly of the *m*-compound. This mixture is not easily resolved into its components by distillation, therefore the individual cresols are prepared from the corresponding amino-compounds or sulphonic acids. The antiseptic action of the cresols is greater than that of phenol; the mixture of crude cresols from tar emulsified with soap is used as a disinfectant (*lysol*).

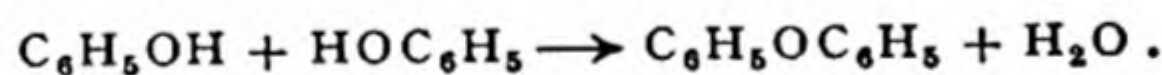
On oxidation, cresols are completely destroyed; if however the hydrogen of the hydroxyl group is replaced by alkyl or acetyl, they can be oxidised like toluene to the corresponding acids. Like phenol, the cresols react with bromine water.

para-Cresol $\text{C}_6\text{H}_4(\text{CH}_3)\text{OH}$ is produced in the decomposition of proteins and occurs in urine as the sulphate ester.

Thymol, hydroxycymene $\text{C}_6\text{H}_3(\text{CH}_3)(\text{OH})[\text{CH}(\text{CH}_3)_2]$, m.p. 50° , occurs in oil of thyme; it is sparingly soluble in water and is used in medicine as an antiseptic.

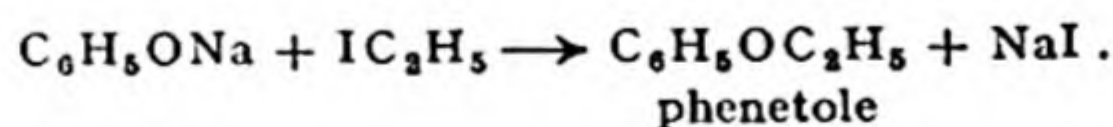
231. *Ethers of phenol.* Purely aromatic ethers like *diphenyl ether*, $\text{C}_6\text{H}_5\text{OC}_6\text{H}_5$, are distinguished from aromatic-aliphatic ethers, *e.g.* *anisole*, $\text{C}_6\text{H}_5\text{OCH}_3$.

Diphenyl ether is obtained by passing phenol vapour over hot thorium oxide (SENDERENS):

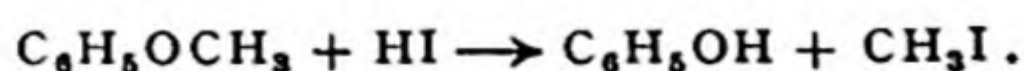


This compound can also be prepared by heating bromobenzene and potassium phenate with finely divided copper at about 210° (ULLMANN).

Mixed ethers are prepared by heating sodium phenate with an alkyl halide (or better with dimethyl sulphate):



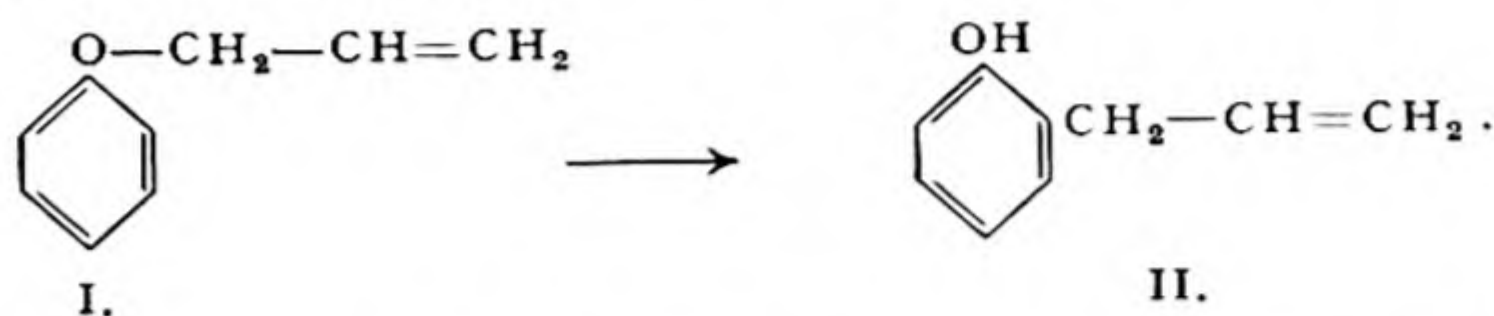
Properties. Both mixed and aromatic ethers are pleasant smelling, stable substances. Diphenyl ether is not split even by heating with hydriodic acid at 250° . On heating mixed ethers to a high temperature with halogen hydracids, phenol and an alkyl halide are formed, *e.g.*:



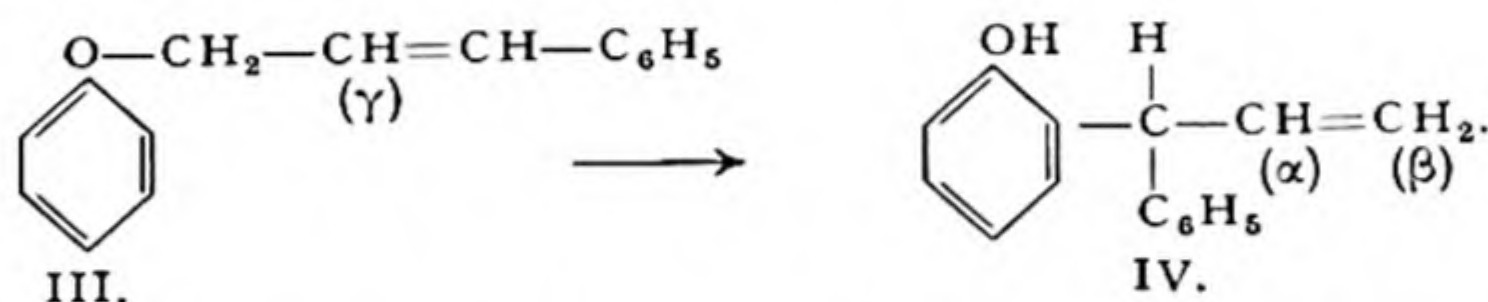
Anisole and phenetole are liquids boiling at 155° and 172° , respectively; the higher boiling point of phenol (181°) is to be ascribed to association in the liquid phase.

The hydrogen atoms of the nucleus may be substituted in these compounds also.

The allyl ether of phenol (I) passes over on boiling into the isomeric *o*-allylphenol (II); this transformation occurs also with allyl ethers of substituted phenols. If the *o*-position is occupied, the allyl group enters the *p*-position:



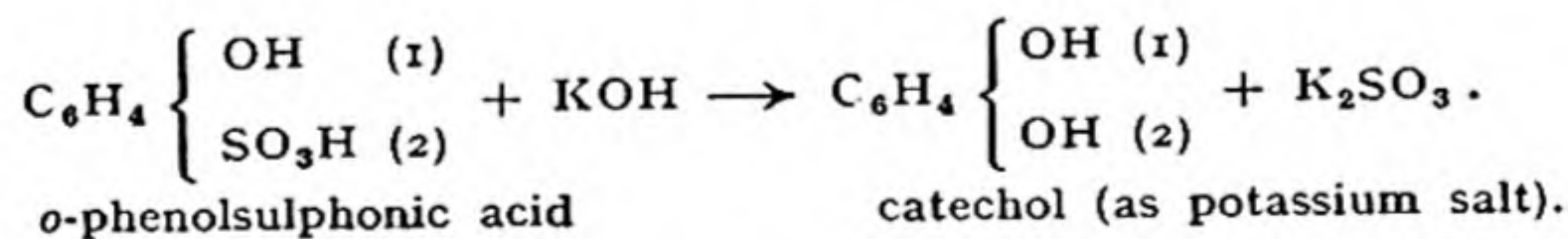
This reaction is known after its discoverer as the *CLAISEN transformation*. Ethers in which the allyl group is substituted in the γ -position are converted on heating into 2-(α -substituted allyl) phenols, *e.g.* phenyl cinnamyl ether (III) gives *o*-(α -phenylallyl)phenol IV:



The structure of IV follows for example, from the oxidative degradation of the compound by ozone, in which formaldehyde is produced but not benzaldehyde. The carbon atom entering the benzene ring in the *CLAISEN* transformation is not the carbon atom in the allyl ether attached to oxygen, but is usually the γ -carbon atom and sometimes the β -carbon atom.

232. Higherhydric phenols are more readily soluble in water than phenol; they react more easily with oxidising agents than the mono-hydric phenols. Many of them may be used as powerful reducing agents when dissolved in caustic potash.

Di-hydric phenols or dihydroxybenzenes. The *o*-compound, *catechol*, $\text{C}_6\text{H}_4 \begin{Bmatrix} \text{OH (1)} \\ \text{OH (2)} \end{Bmatrix}$, is prepared by fusing *o*-phenolsulphonic acid or *o*-chlorophenol with potash:



Catechol melts at 104° and is very readily soluble in water, alcohol and ether. It is found as a decomposition product from various vegetable products, including catechin (264) from which it derives its name. A solution in water precipitates the metal from a solution of silver nitrate at ordinary temperatures; it gives a green coloration with ferric chloride. A character-

istic reaction of catechol is the formation of an insoluble lead salt on the addition of lead acetate.

Guaiacol, the monomethyl ether of catechol, $C_6H_4 \begin{Bmatrix} OCH_3 & (1) \\ OH & (2) \end{Bmatrix}$, which was first observed amongst the distillation products of guaiacum resin, occurs in large quantities in beech-tar. It is used in medicine.

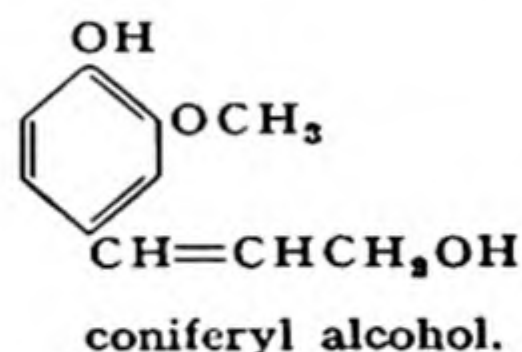
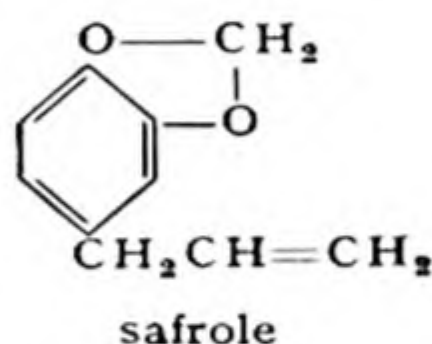
Veratrole, the dimethyl ether of catechol, $C_6H_4 (OCH_3)_2$, is obtained as a degradation product from various natural products.

Eugenol, $C_6H_3(OH)(OCH_3)CH_2CH=CH_2$, is the odiferous principle of cloves (*Eugenia caryophyllata*); it boils at 252° . It serves as the starting product for the preparation of vanillin (258). On heating with potassium hydroxide solution, eugenol is isomerised to *isoeugenol*, $C_6H_3(OH)(OCH_3)CH=CHCH_3$, the double bond being displaced in this reaction.

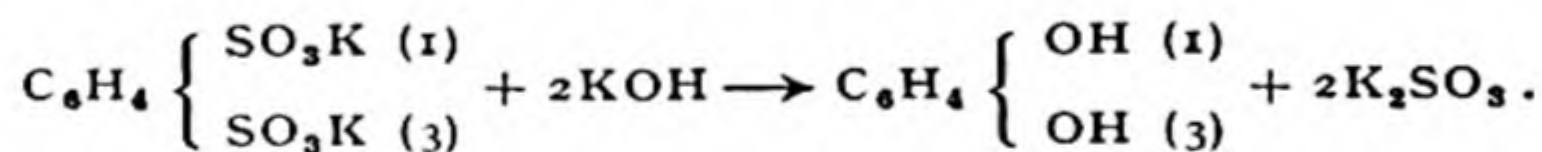
Isoeugenol occurs in nutmeg oil as well as in other products.

Safrole is a derivative of catechol occurring, for example, in the essential oil of *Sassafras officinale* and in oil of camphor.

Coniferyl alcohol occurs in the form of a glucoside, *coniferoside*, in the cambium of conifers:



Resorcinol, *m*-dihydroxybenzene $C_6H_4 \begin{Bmatrix} OH & (1) \\ OH & (3) \end{Bmatrix}$, is prepared by fusing potassium benzene-*m*-disulphonate with potash:



Resorcinol melts at 118° and is readily soluble in water, alcohol and ether. An aqueous solution gives a deep violet colour with ferric chloride; 2,4,6-tribromoresorcinol is formed with bromine water at ordinary temperatures. For a delicate reaction for resorcinol reference should be made to 276.

A homologue of resorcinol, *orcinol* $C_6H_3 \begin{Bmatrix} OH & (1) \\ OH & (3) \\ CH_3 & (5) \end{Bmatrix}$, is a constituent of lichens.

The colouring matters of litmus and orchil are derivatives of orcinol.

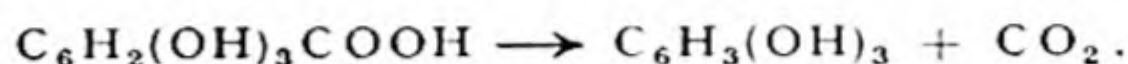
Quinol, *hydroquinone*, *p*-dihydroxybenzene $C_6H_4 \begin{Bmatrix} OH & (1) \\ OH & (4) \end{Bmatrix}$, was first obtained by PELLETIER and CAVENTOU by the dry distillation of quinic acid (233). It is prepared by reducing quinone (233) and is easily reconverted into this substance by oxidation. Hydroquinone is a reducing agent, which precipitates silver from a solution of silver nitrate at ordinary temperatures; its use as

a photographic developer depends on this reducing power. A glucoside of quinol, namely, *arbutin*, $p\text{-HOC}_6\text{H}_4\text{OC}_5\text{H}_{10}\text{O}_5$, occurs in some plants (*e.g.* in *Arctostaphylos uva ursi* or bearberry).

Of the *trihydric phenols* or *trihydroxybenzenes*, two isomers will be discussed.

Pyrogallol, 1,2,3-trihydroxybenzene, $\text{C}_6\text{H}_3 \begin{cases} \text{OH} & (1) \\ \text{OH} & (2) \\ \text{OH} & (3) \end{cases}$, was obtained by SCHEELÉ

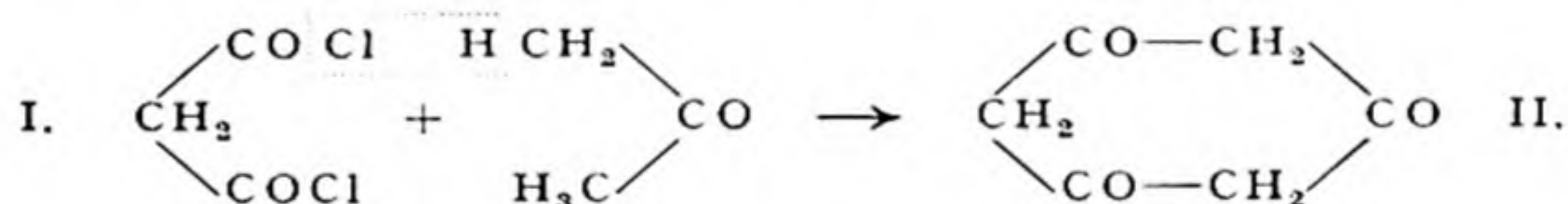
as early as 1786 by heating gallic acid (263) which, when decarboxylated, gives carbon dioxide in the process:



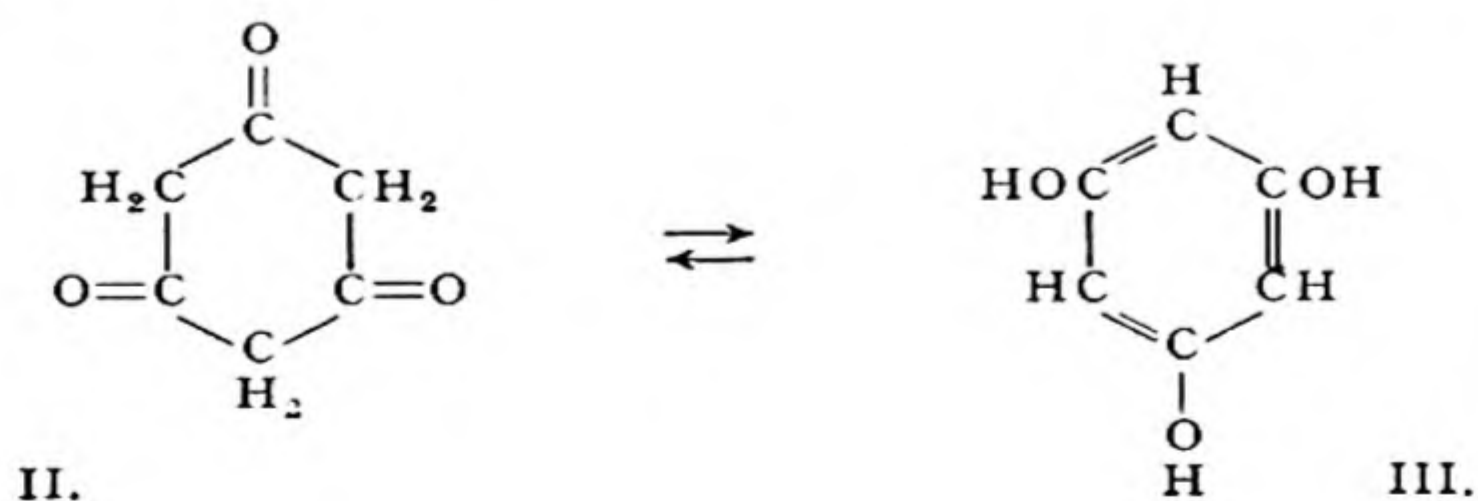
Pyrogallol is readily soluble in water and melts at 132° ; in alkaline solution it is a very powerful reducing agent, for example, it readily absorbs oxygen from the air (becoming brown in colour) and is therefore used in gas analysis. It is also used as a photographic developer.

Phloroglucinol, 1,3,5-(*symm.*)-trihydroxybenzene, $\text{C}_6\text{H}_3 \begin{cases} \text{OH} & (1) \\ \text{OH} & (3) \\ \text{OH} & (5) \end{cases}$, is found

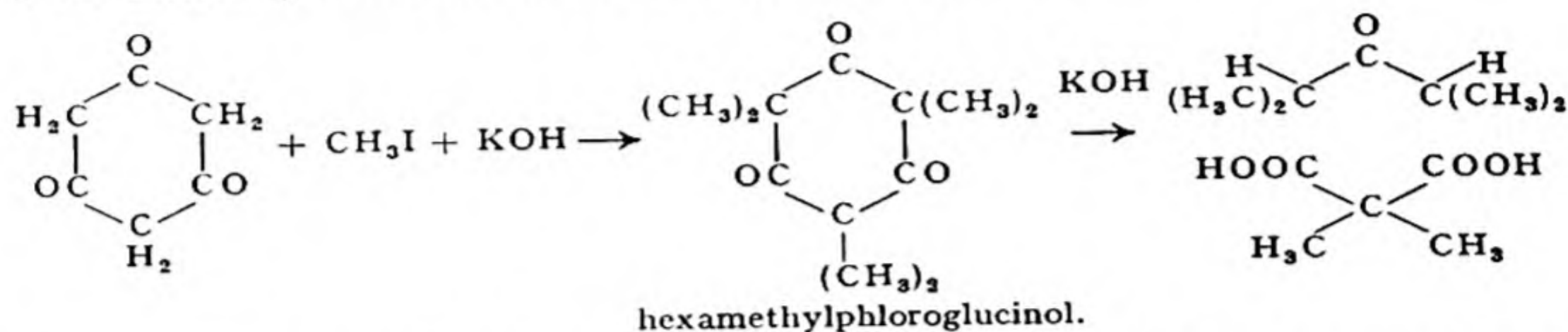
amongst the decomposition products of various vegetable substances, *e.g.* of a glucoside (179) *phlorizin* occurring in the bark of apple trees. Phloroglucinol can be obtained from aliphatic substances by the following synthesis. By heating malonyl chloride (I) and acetone in equivalent quantities with the addition of calcium carbonate as an acid binding agent to take up the hydrochloric acid liberated in the reaction, a condensation product is produced, which is converted almost quantitatively into phloroglucinol (II) on continued heating with water and calcium carbonate:



According to this reaction scheme phloroglucinol should have structure II, a cyclohexane derivative (287) in which three methene groups (CH_2) are replaced by three carbonyl (CO) groups; it should therefore be called *cyclohexane-1,3,5-trione*. Indeed phloroglucinol can react as if it had this structure; for example, it can react with three molecules of hydroxylamine to give a trioxime:



Phloroglucinol also has the character of a phenol; with acetyl chloride it gives a triacetate and with diazomethane (210) a trimethyl ether. It can therefore react in tautomeric forms, namely, as a cyclohexane derivative (II) and as a trihydroxybenzene (III). On treating phloroglucinol with potash and methyl iodide a hexamethyl-derivative is produced, the hydrogen atoms of the methene groups being substituted by CH_3 . This compound is easily broken down by alkali in the same way as the 1,3-diones, with the production of dimethylmalonic acid and *tetramethylacetone*:

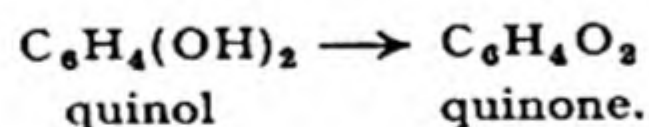


In the ultraviolet, phloroglucinol shows approximately the same absorption band as its trimethyl ether. Phloroglucinol can be recovered from this ether by boiling with hydrochloric acid, from which it follows that the methyl groups are attached to oxygen. From the agreement in the absorption spectra of phloroglucinol and the trimethyl ether it may be concluded that phloroglucinol exists mainly in the enol form III. In agreement with this is the fact that the absorption band for phloroglucinol lies at approximately the same wave-lengths as that for pyrogallol, where there can be no question of tautomerism occurring.

A much smaller absorption in the ultraviolet would be expected for a cyclohexanetrione (compare the extinction curves for cyclohexanone and cyclohexanedione in Fig. 58).

(b) Quinones

233. The name *quinones* refers to compounds derived from aromatic dihydroxy-compounds by the loss of the two hydroxylic hydrogen atoms, thus:

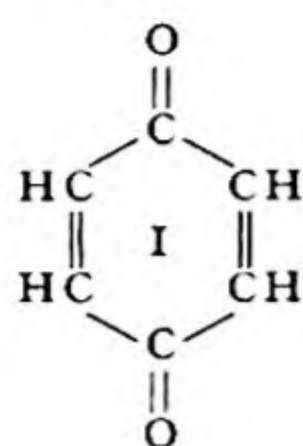


The simplest quinone is *p*-benzoquinone, which is usually called quinone and is produced by the oxidation of quinol.

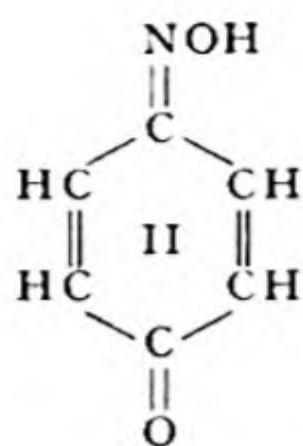
Benzoquinone was first obtained by WOSKRESENZKY in 1838 as an oxidation product of *quinic acid*, a substance occurring in cinchona bark and having a molecule comprising a cyclohexane ring substituted by hydroxyl groups and a carboxyl group. The name quinone is derived from this source.

GRAEBE (1867) considered quinones to be compounds of the type $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array}$,

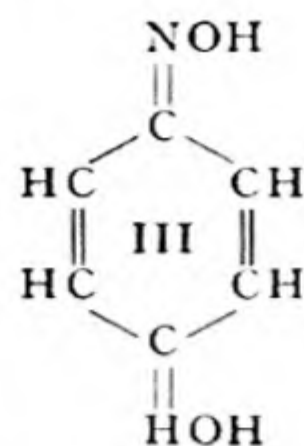
which explained the connection with quinol and the oxidising action of the quinones; at the present time, formula I is preferred, because with hydroxylamine hydrochloride, first a monoxime II and then a dioxime III is produced.



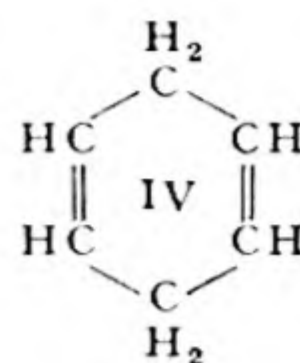
quinone



quinone monoxime

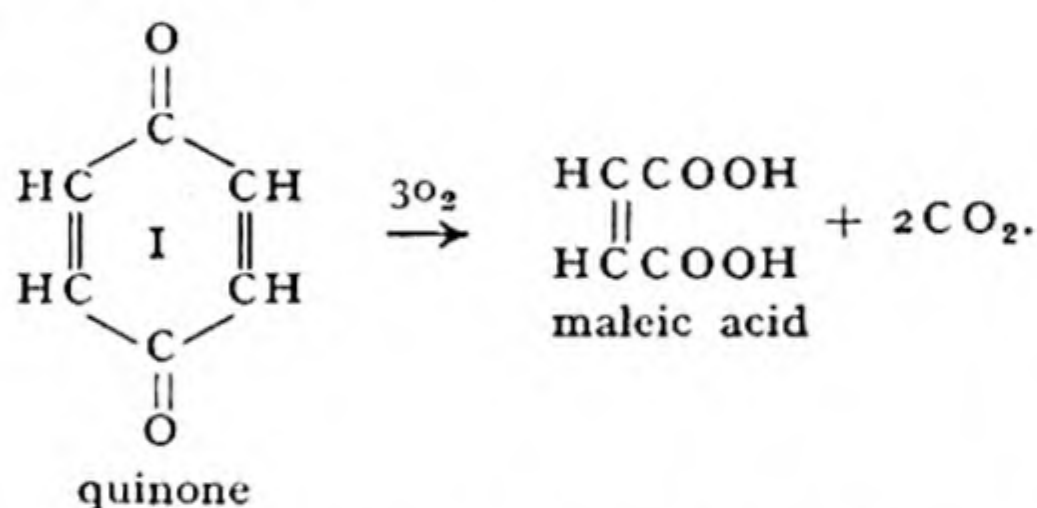


quinone dioxime



cyclohexadiene.

The presence of double bonds in quinone is shown by the addition of two molecules of bromine to quinone dissolved in chloroform. On oxidising quinone with, for example, alkali persulphate, $K_2S_2O_8$, in a solution of sulphuric acid containing a little silver sulphate, maleic acid and a little fumaric acid are produced. Hence quinone does not show the properties of a derivative of benzene; it is to be regarded as the *p*-diketone of cyclohexadiene IV:



Benzoquinone is produced by the oxidation of many *para*-derivatives of benzene, including *p*-aminophenol (241), quinol, sulphanilic acid (241), *p*-phenolsulphonic acid (234), etc. It is prepared, however, by oxidising aniline (236) with sodium bichromate and sulphuric acid.

At the beginning of the reaction an insoluble greenish black dyestuff is formed related in structure to *pernigraniline* (238) and quinone is produced from this substance by further oxidation. Black colouring matters are formed as by-products. (Compare p. 382).

Quinone is yellow in colour, it has an irritating odour, is volatile in steam and can be sublimed. It has oxidising properties and can easily be reduced,

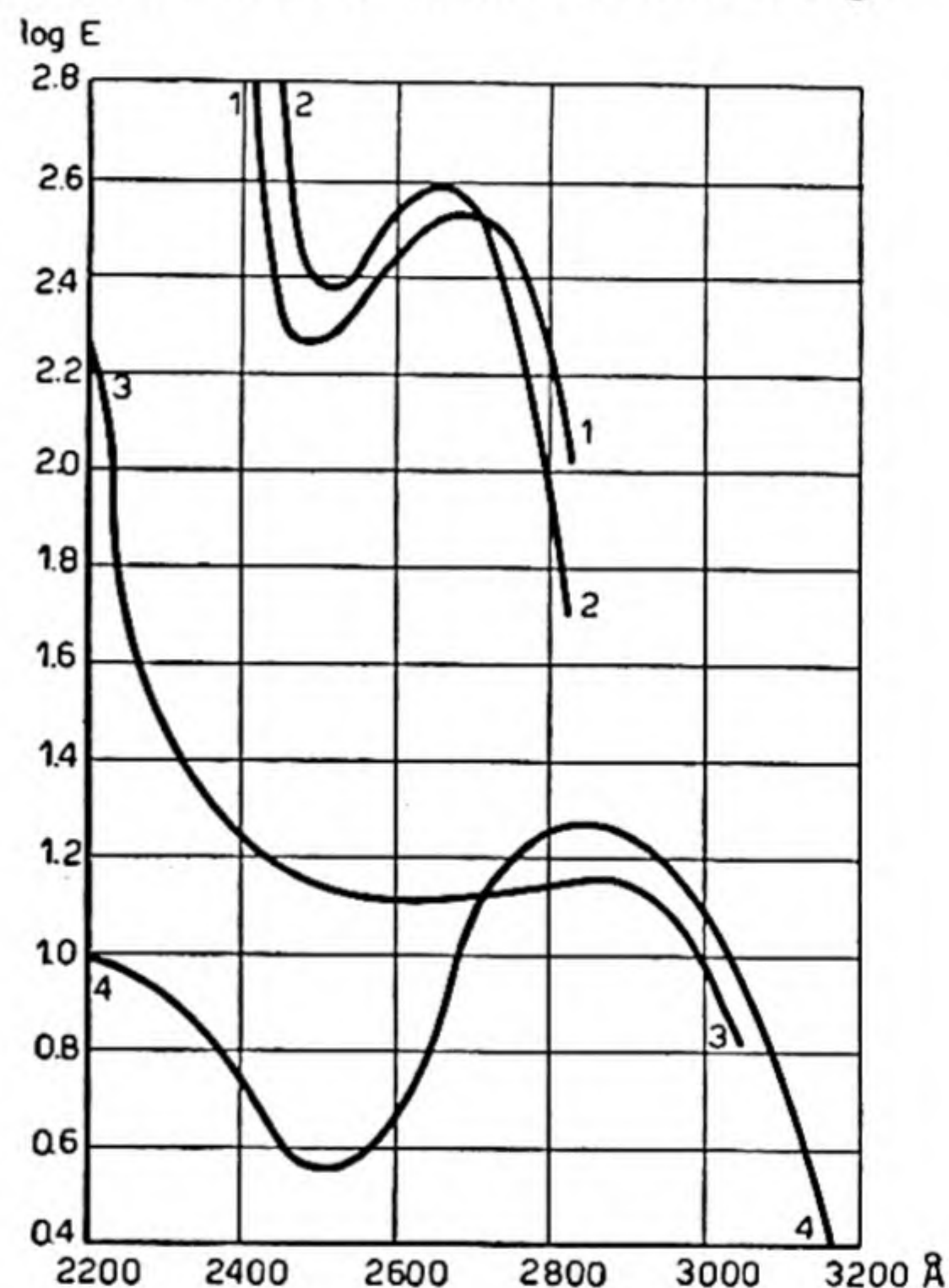
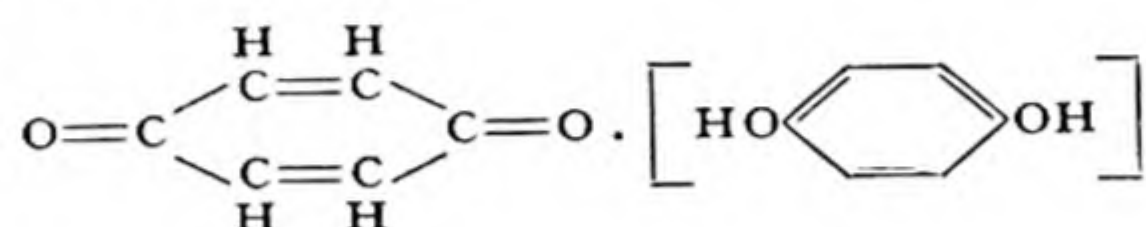


Fig. 58.
Absorption curves in the ultra-violet
1 = phloroglucinol
2 = phloroglucinol trimethyl ether
3 = cyclohexanedione
4 = cyclohexanone

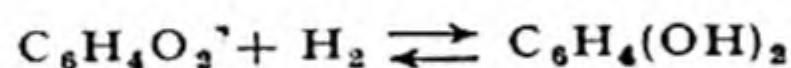
e.g. with sulphur dioxide to quinol (232). A number of *para*-quinones, made like quinone itself by the oxidation of *p*-dihydroxy-compounds, are known. They are usually yellow in colour, they have an irritating odour, they are very volatile in steam by which they are partly decomposed and they have oxidising properties. With regard to quinone monoxime see 235.

When quinol is oxidised in aqueous solution with an insufficient quantity of ferric chloride to convert it into quinone, dark green, metallic looking crystals of *quinhydrone* separate; this substance may also be produced from equimolecular amounts of quinone and quinol. Quinhydrone dissolves in alcohol or benzene with a yellow colour and in these solutions it is to a large extent dissociated into its components; it is completely dissociated in boiling water. Quinhydrone was therefore formulated as a molecular compound of quinol and quinone:

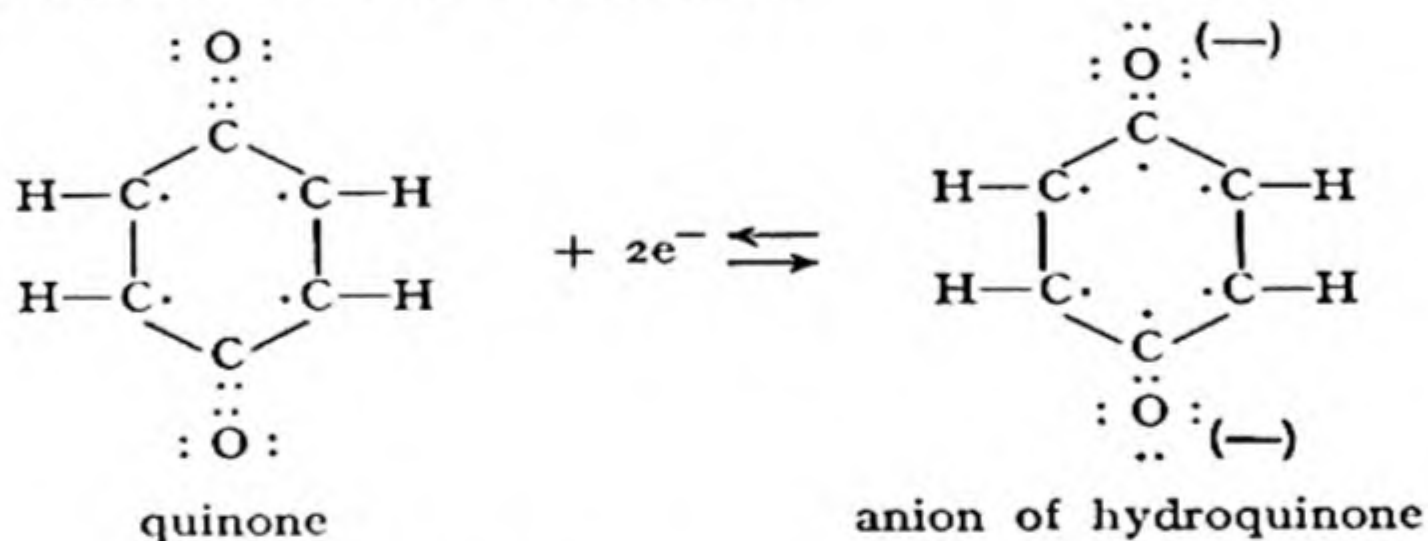


A coloured addition compound of 1 mol. of quinone and 2 mols. of phenol is also known. Probably, crystalline quinhydrone is a polymer built up from a large number of molecules of quinone and quinol; the intense colour is bound up with the occurrence of mesomeric forms.

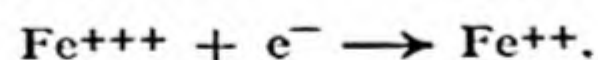
The reduction of quinone to hydroquinone is a reversible reduction-oxidation reaction:



or expressed in electronic formulae (in which not all of the valency electrons are given and each bond corresponds to two electrons):

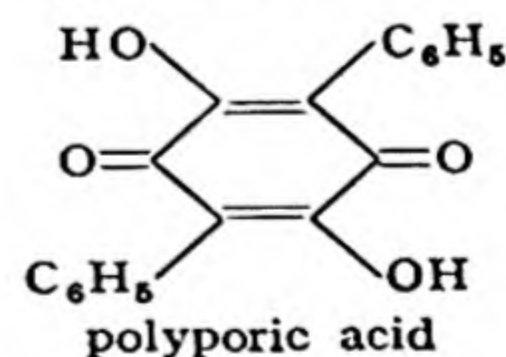


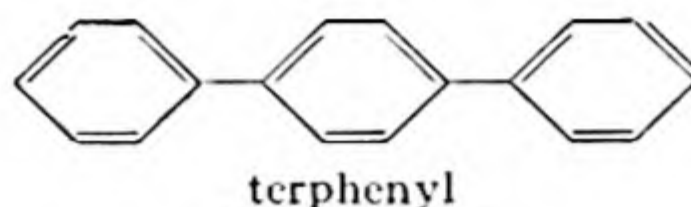
Each of the oxygen atoms in the hydroquinone anion carries a negative charge. The electrochemical process is comparable with the conversion of a ferri-ion into a ferro-ion:



From recent researches of KÖGL it appears that some colouring matters from moulds or fungi like *polyporic acid*, a brownish yellow substance occurring in species of *polyporus*, are derivatives of 2,5-diphenylbenzoquinone; the potassium and ammonium salts are intense violet in colour.

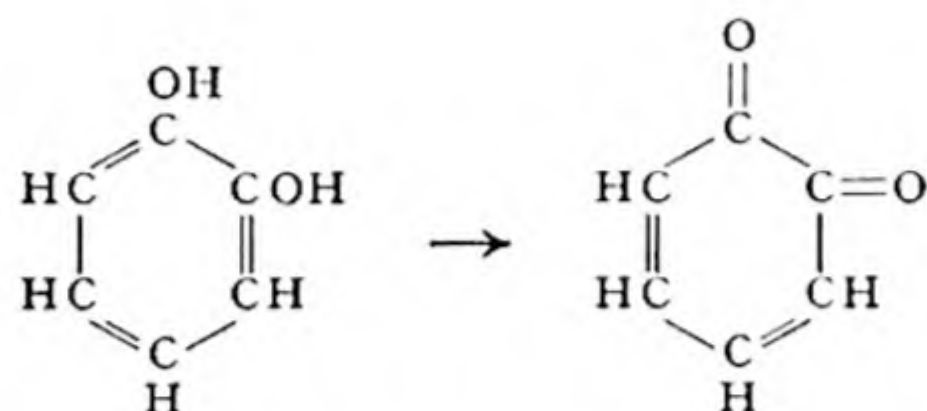
Oxidation of polyporic acid produces benzoic acid. The presence of two hydroxyl groups follows from the formation of a diacetyl derivative, while distillation with zinc dust produces *terphenyl*:





The structure of polyporic acid deduced from this reasoning has been confirmed by synthesis.

ortho-Benzoquinone is produced by oxidising catechol with silver oxide in dry ether:



It is a very unstable, volatile, odourless compound, which is obtained in red needles.

Resorcinol cannot be converted into a quinone. From an examination of the structural formulae of *o*- and *p*-quinones it is seen that a similar formula for a *m*-quinone cannot be constructed.

(c) *Substituted phenols*

234. Halogenophenols. *o*- and *p*-chlorophenol and the corresponding bromophenols are produced by chlorinating and brominating phenol. The reaction takes place without the addition of a catalyst. When the reaction is carried out in aqueous solution di- and tri-substitution products are formed (see the formation of tribromophenol 229). The iodination of phenol can be carried out by the action of iodine in the presence of an oxidising agent like iodic acid, which serves to oxidise the hydriodic acid as it is formed.

The halogen atoms can be replaced by hydroxyl groups by fusion with potash. In this reaction the entering hydroxyl group may sometimes take up another position to that occupied by the halogen atom, as in the replacement of a sulpho-group by hydroxyl. On account of the presence of the halogen atom, the halogenophenols have stronger acid characteristics than phenol; for example, carbonates are decomposed by trichlorophenol. The halogenophenols have strong antiseptic properties and for this reason, various compounds of this group, *e.g.* *p*-chlorophenol, tribromophenol and *p*-chloro-*m*-cresol, are used as disinfectants. *o*-Halogenophenols have a very penetrating odour resembling that of iodoform.

Phenolsulphonic acids. *o*- and *p*-phenolsulphonic acids are produced when phenol is sulphonated; *o*-phenolsulphonic acid is unstable and gives a violet

TABLE 45
MELTING AND BOILING POINTS OF SOME HALOGENO-PHENOLS

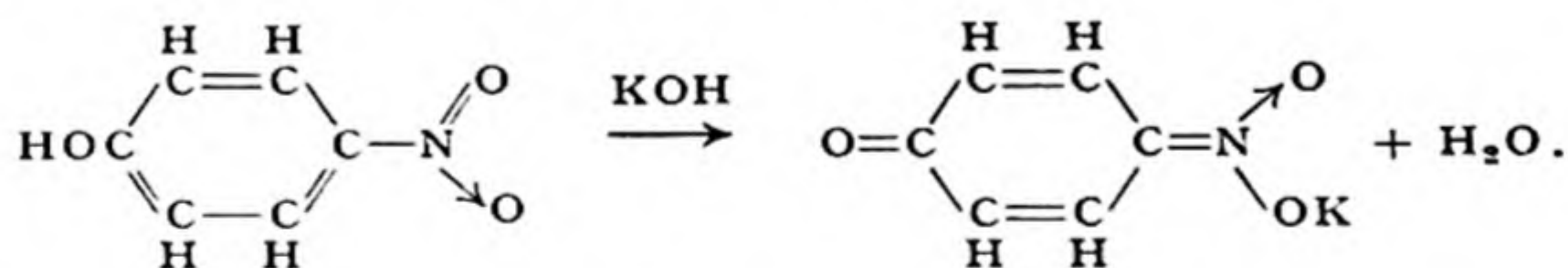
	Melting point	Boiling point
<i>o</i> -Chlorophenol	8.7°	176°
<i>m</i> -Chlorophenol	32.8°	214°
<i>p</i> -Chlorophenol	42.9°	217°
<i>o</i> -Bromophenol	5.6°	195°
<i>m</i> -Bromophenol	33°	236°
<i>p</i> -Bromophenol	63.5°	238°
2,4,6-Tribromophenol	92.5°	—
<i>o</i> -Iodophenol	40.4°	187°/100 mms.
<i>m</i> -Iodophenol	40°	—
<i>p</i> -Iodophenol	92°	—

colouration with ferric chloride; *p*-phenol sulphonic acid gives a very faint reaction.

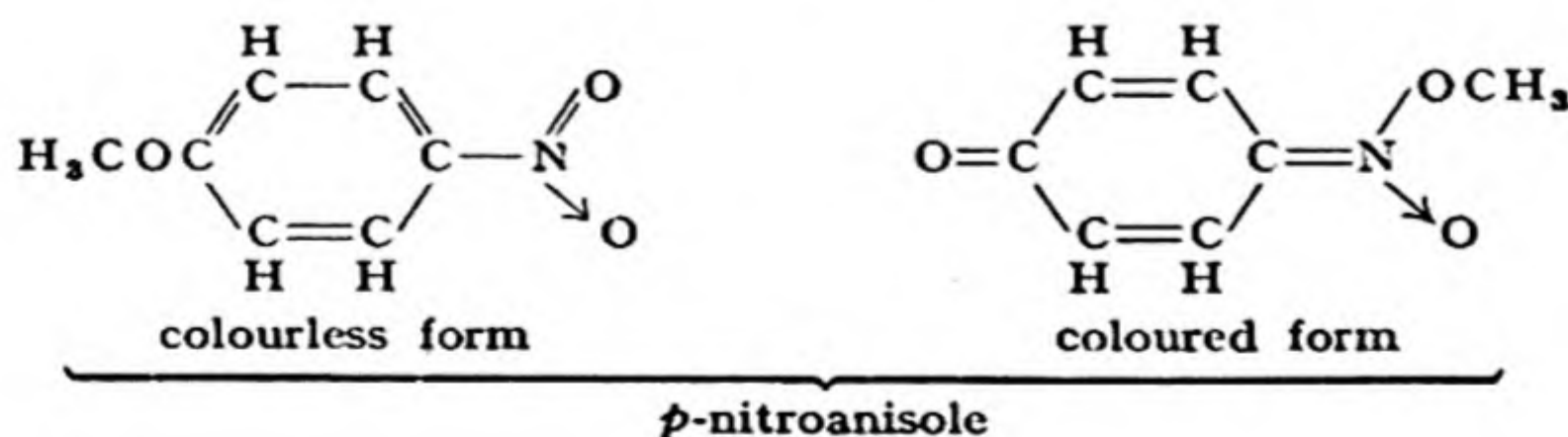
235. Nitrophenols. *o*- and *p*-Nitrophenols are produced by the action of dilute nitric acid on phenol at ordinary temperatures. The isomers are separated by steam distillation, the *o*-compound passing over with the distillate, the *p*-compound remaining behind.

o-Nitrophenol is yellow and melts at 45°. It has a characteristic odour and is used for the preparation of *o*-aminophenol and *o*-nitroanisole. *p*-Nitrophenol is odourless and melts at 114°.

p-Nitrophenol is colourless but dissolves in alkali with a yellow colour. This phenomenon occurs with many nitrophenols. Probably this is due to a tautomeric form, the "*aci-form*" from which the salt is derived:



Another argument in favour of this opinion is that nitrophenyl ethers exist in two isomeric forms one of which is colourless and the other coloured (HANTZSCH, see also 226).



m-Nitrophenol is obtained from *m*-nitraniline (240) by diazotisation (245).

2,4,6-Trinitrophenol or *picric acid* is prepared by nitrating phenol with a mixture of concentrated nitric and concentrated sulphuric acids. It may also be obtained by heating benzene with nitric acid and mercuric nitrate; under these conditions benzene is oxidised to phenol which is then nitrated to picric acid. Picric acid cannot be further nitrated, so that it is the final product in the nitration of phenol. It was obtained in 1788 by HAUSMANN by the action of nitric acid on indigo; in 1799 WALTER obtained the same substance by treating silk with nitric acid. The name picric acid was given by DUMAS (πικρος = bitter).

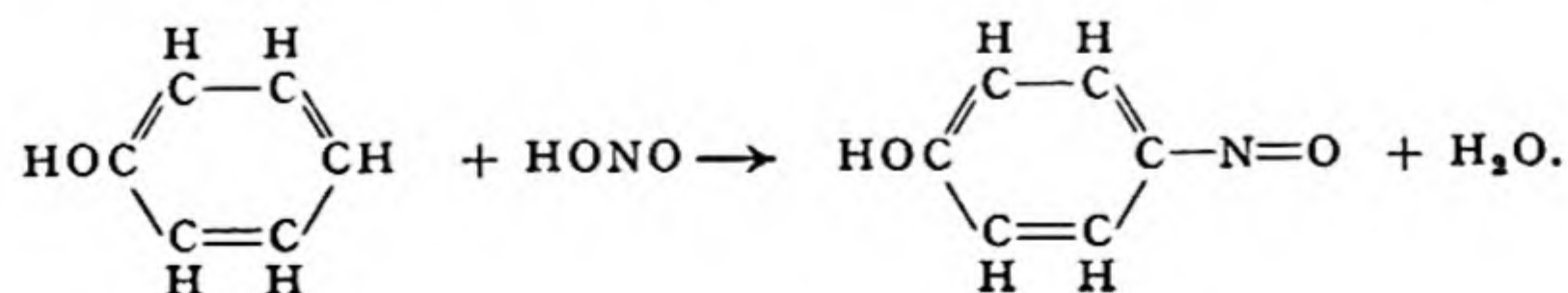
Picric acid melts at 122° and is pale yellow when pure, although its aqueous solution is deep yellow; since it is fairly strongly ionised in water ($k = 0.38$), the yellow colour is due to the anion, which is converted into a tautomeric form. A solution of picric acid in petroleum ether, in which it is not ionised, is colourless. Picric acid has an intensely bitter taste.

In chemical behaviour picric acid is similar to a carboxylic acid; the hydroxyl group is replaced by chlorine by phosphorus pentachloride with the production of picryl chloride, which behaves like an acid chloride (75). The methyl ether, which is produced from silver picrate and methyl iodide, has the properties of an ester, for this compound can be hydrolysed by boiling with alkali and it is converted into picramide by ammonia. From this it is clear that the reactivity of a fourth substituent is increased by nitro-groups in the two *o*- and the *p*-positions.

The well defined crystalline potassium and ammonium salts of picric acid explode violently when struck; the acid itself can be caused to explode by mercury fulminate (157) or another priming explosive or detonator. Picric acid and ammonium picrate are used on a large scale as explosives.

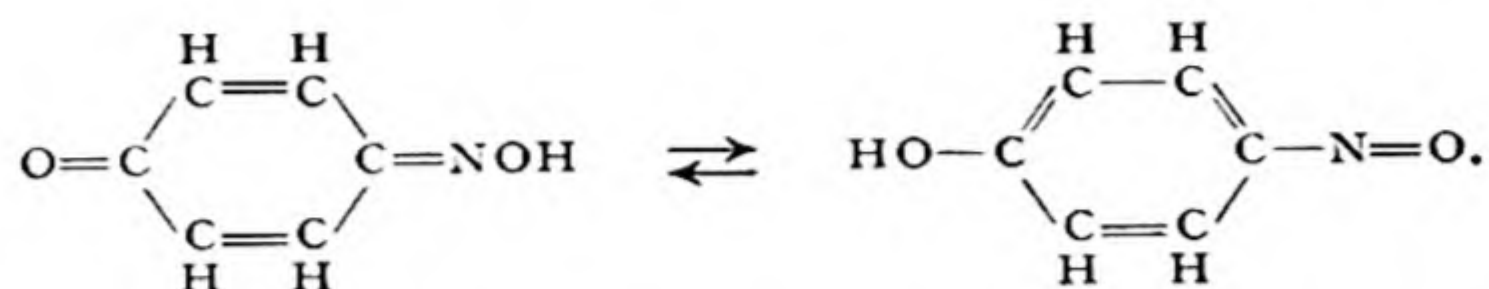
Picric acid gives well defined crystalline picrates with heterocyclic bases and alkalis; the bases can be liberated from picrates by means of ammonia or alkalis which are frequently used for identifying them. Picric acid also gives well defined addition compounds with various aromatic hydrocarbons, *e.g.* with naphthalene, $C_{10}H_8$, a compound $C_{10}H_8[C_6H_2(NO_2)_3OH]$, m.p. 149°, is formed. These double compounds are frequently used for the separation and identification of aromatic hydrocarbons. Picric acid can be detected by adding potassium cyanide to the aqueous solution, when the latter assumes a red colour due to the formation of *isopurpuric acid*.

p-Nitrosophenol, m.p. 128°, is produced by the action of nitrous acid on phenol:



It is decomposed by heat and reacts on oxidation and reduction in accordance with the above formula, since *p*-nitrophenol and *p*-aminophenol respectively, are produced.

Nitrosophenol is identical with quinone monoxime (233), *i.e.* this is a case of a tautomeric conversion of a quinone derivative into an aromatic compound:



The nitroso-form and the oxime-form have not been isolated as individuals; isomeric N- and O-ethers, however, derived from the two forms, are known.

(viii) AROMATIC AMINES

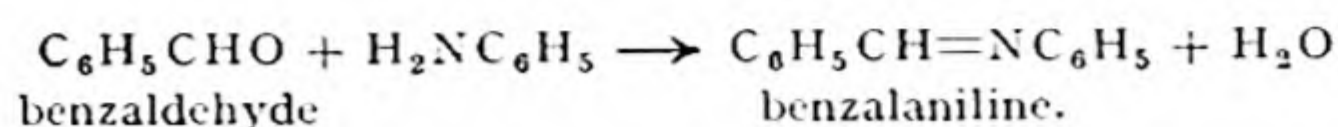
236. *Monoamino-compounds* are produced by reduction of the corresponding nitro-compounds. This reduction may be carried out with tin and hydrochloric acid, iron filings and dilute sulphuric or hydrochloric acid or by gaseous hydrogen with an appropriate catalyst. Nitro-compounds may also be reduced electrolytically (244). Aromatic amines are very feeble bases compared with aliphatic amines (49). They do not turn red litmus blue and aqueous solutions are practically non-conducting. They give salts which react acid in aqueous solution due to partial hydrolysis. The negative effect of the phenyl group on the amino-group is clearly noticeable here. This is particularly marked with di- and tri-phenylamine. Diphenylamine is still able to form salts with strong acids, which are completely dissociated in water; in triphenylamine ability to form salts has practically disappeared.

Under the influence of the amino-group, the hydrogen atoms of the benzene nucleus are more easily substituted (229, compare the effect of the hydroxyl group). 2,4,6-Tribromoaniline is produced immediately from aniline, $\text{C}_6\text{H}_5\text{NH}_2$, and bromine water. The amines are much more readily oxidised than aromatic hydrocarbons. The hydrogen atoms attached to nitrogen in *primary* and *secondary* aromatic amines can be replaced by alkyl by treatment with alkyl halides as with aliphatic amines, secondary or tertiary amines being produced, *e.g.*:



The primary amines are acetylated by acetic anhydride; similar acyl-derivatives are obtained by heating primary aromatic amines with anhydrous acids. These compounds, called *anilides*, are split up into their components by boiling with dilute alkalis or with mineral acids.

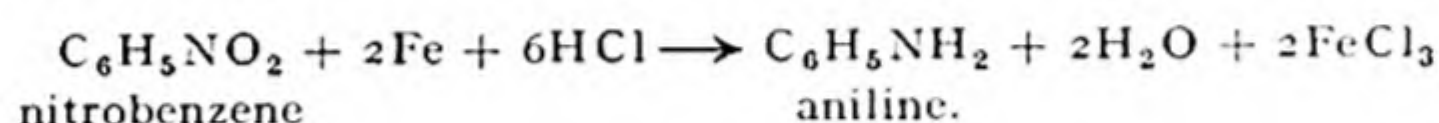
Primary amines react with aromatic aldehydes as follows:



They give the carbylamine reaction (56) and diazonium compounds (245) are produced with nitrous acid.

Aniline $\text{C}_6\text{H}_5\text{NH}_2$, the first member of this homologous series, was first obtained by heating indigo with lime (UNVERDORBEN, 1826). The name aniline is derived from the Spanish word for indigo, namely, *añil* (FRITZSCHE). In 1843, A. W. HOFMANN found that this aniline was identical with the reduction product of nitrobenzene.

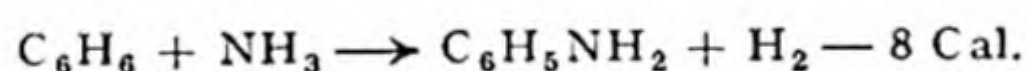
It is prepared commercially by reducing nitrobenzene with iron turnings and hydrochloric acid:



Very much less (1/40th part only) hydrochloric acid is required in practice for this reduction than given by the above equation; this is due to the fact that ferric chloride is hydrolysed by water giving ferric oxyde and hydrochloric acid which takes part in the reaction again.

The catalytic reduction of nitrobenzene to aniline is carried out on a technical scale with the aid of finely divided copper or silver catalysts. The preparation of aniline from chlorobenzene (220) and ammonia is also carried out on a commercial scale.

Of theoretical interest is the formation of small quantities of aniline by the action of ammonia on benzene at 500° in the presence of finely divided iron or nickel (WIBAUT):



Aniline is a colourless liquid, which becomes brown in colour on exposure to air due to the presence of very small quantities of impurities. Aniline and its homologues are very slightly soluble in water.

With formaldehyde, it gives a condensation product, *anhydroformaldehyde-aniline*, $(\text{C}_6\text{H}_5\text{N}=\text{CH}_2)_3$, which is very sparingly soluble in water.

An aqueous solution of aniline is coloured violet by bleaching powder; this is an extremely sensitive and specific reaction. The initial reaction product is probably *phenylchloramine* $\text{C}_6\text{H}_5\text{NHCl}$, in the same way that chloramine, NH_2Cl , is produced from ammonia and sodium hypochlorite; the phenylchloramine then reacts further with aniline with the formation of coloured products. An acid solution of an aniline salt is coloured by potassium bichromate, first dark green and then black and a black dyestuff, *aniline black* (238), separates from the solution.

Homologues of aniline, the *toluidines* and the *xylidines*, are produced by reduction of the corresponding nitro-compounds. *Ortho*- and *para*-toluidines

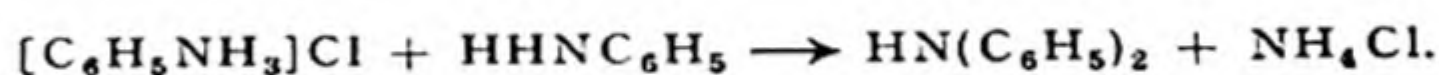
can be separated from one another via their oxalates, which have different solubilities in water.

Aniline and its homologues are poisonous.

TABLE 46
SOME PHYSICAL CONSTANTS OF ANILINE AND ITS HOMOLOGUES

Name	Formula	Boiling point	Melting point	d_4^{20}
Aniline	$C_6H_5NH_2$	184°	— 6.2°	1.0216
<i>o</i> -Toluidine	$CH_3C_6H_4NH_2-1,2$	201°	—16.1°	0.9989
<i>m</i> -Toluidine	$CH_3C_6H_4NH_2-1,3$	203°	—31.0°	0.9891
<i>p</i> -Toluidine	$CH_3C_6H_4NH_2-1,4$	200°	43.7°	
asymm. Xylidine	$(CH_3)_2C_6H_3NH_2$ 1,2 4	226°	49°	

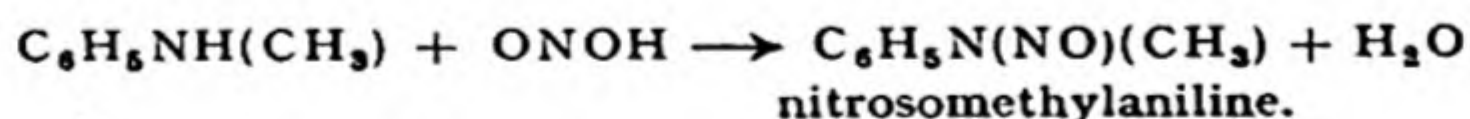
237. Secondary amines. Of the purely aromatic amines, *diphenylamine* $(C_6H_5)_2NH$, may be mentioned. It is produced by heating the corresponding primary amine, aniline, with its hydrochloride:



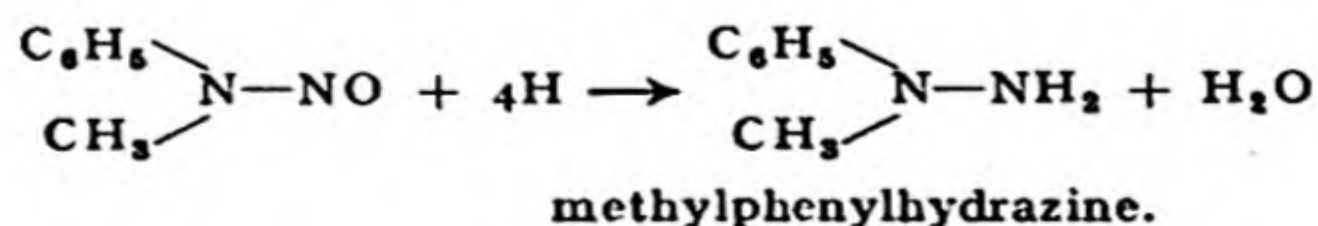
It is used as an extremely sensitive reagent for nitric acid. A few drops of the liquid to be tested are added to a solution of diphenylamine in concentrated sulphuric acid; in presence of nitric acid a very intense blue colour is produced. This reaction is a proof of the presence of nitric acid only when it is certain that no other oxidising agent is present, since diphenylamine gives a blue colour also with bromine water, potassium permanganate and other oxidising agents.

Mixed aromatic aliphatic amines are obtained by the method previously mentioned (p. 376), in which a mixture of secondary and tertiary amines is formed. In order to obtain the secondary amine in a pure state, a hydrogen atom in the amino-group is first replaced by an acyl group, *e.g.* acetyl; the acyl derivative is then treated with an alkyl iodide and the alkylated acyl compound eventually hydrolysed, whereby the acyl group is split off.

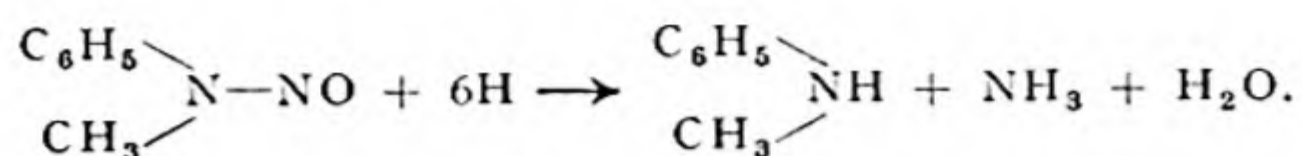
Secondary amines, like their aliphatic counterparts, give *nitrosamines* with nitrous acid:



The nitrosamines can be converted into *hydrazines* (247) by careful reduction:



On powerful reduction, *e.g.* with tin and hydrochloric acid, the nitroso-group is split off:

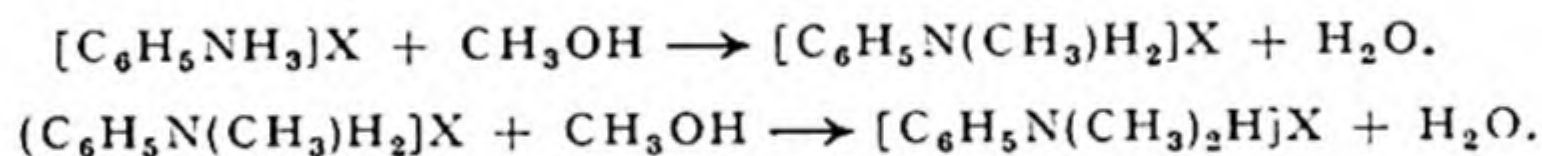


By careful oxidation, nitrosamines can be converted into *nitramines* (152), *e.g.* $\begin{array}{c} \text{C}_6\text{H}_5 \\ \diagdown \\ \text{N}-\text{NO}_2 \\ \diagup \\ \text{CH}_3 \end{array}$. The latter may also be produced by the action of fuming nitric acid on secondary amines like methyl- and ethyl-aniline; in these cases three nitro-groups are introduced simultaneously into the benzene nucleus (VAN ROMBURGH).

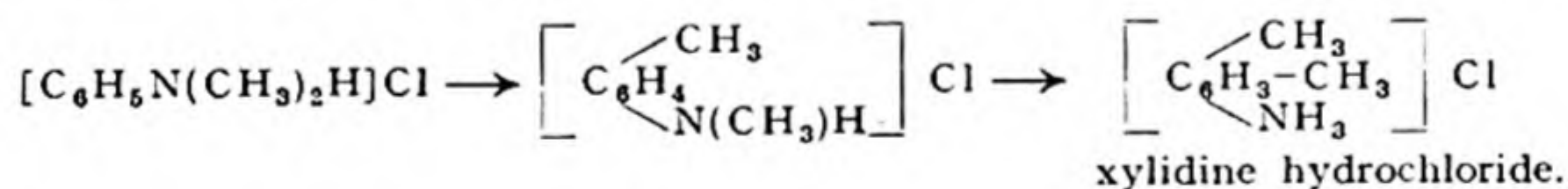
On warming nitrosamines or any other nitroso-compound with phenol in concentrated sulphuric acid, diluting with water and basifying the solution with potash, an intense blue colour is produced (LIEBERMANN reaction).

Tertiary amines. One of the but slightly known, purely aromatic, tertiary amines, is *triphenylamine* $(\text{C}_6\text{H}_5)_3\text{N}$, which is produced by treating diphenylamine with sodium and bromobenzene. It melts at 127° and possesses practically no basic properties.

Mixed aromatic—aliphatic amines, of which *dimethylaniline* $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$, is the most important, are produced by the action of alkyl halides on primary aromatic amines. They are prepared commercially by heating the primary amine salt, usually the sulphate, with the appropriate alcohol in an autoclave. The ratio in which mono- and di-alkylanilines are formed, depends on the amount of alcohol used and on the reaction temperature:

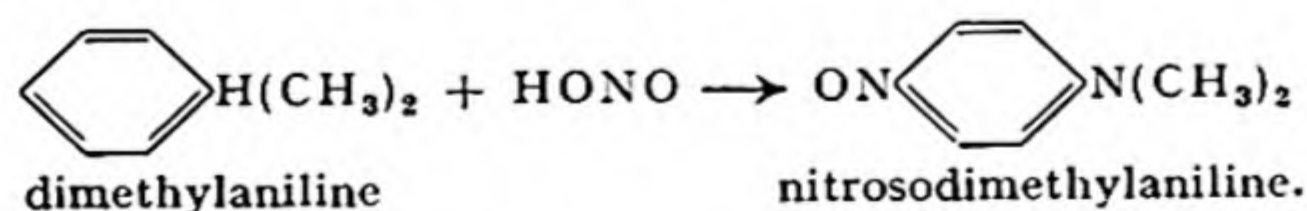


The following changes take place when dimethylaniline hydrochloride is heated in a closed vessel to about 300° (HOFMANN and MARTIUS):



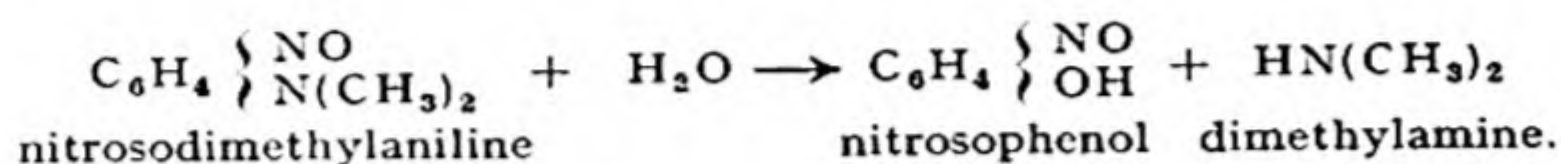
In this reaction which takes place at lower temperatures in presence of zinc chloride, the alkyl group wanders from the nitrogen atom into the nucleus with the formation of a homologue of aniline.

In the dialkylanilines and in dimethylaniline in particular, the hydrogen atom in the *para*-position of the benzene nucleus, is very mobile, *i.e.* very easily displaced by various groups of atoms. Thus dimethylaniline readily gives *nitrosodimethylaniline* with nitrous acid:

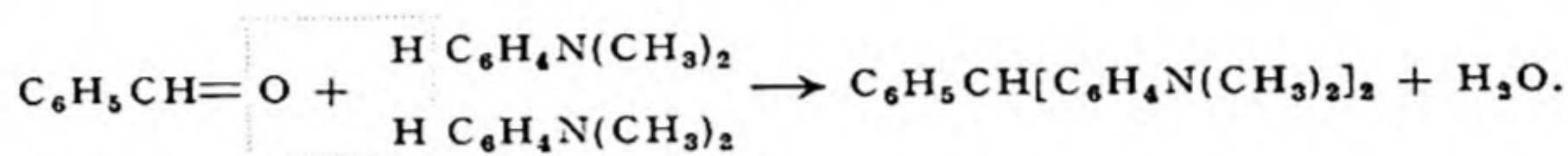


The nitroso-compound crystallises in green leaflets melting at 85° ; its

hydrochloride consists of yellow needles. By oxidation with potassium permanganate, the nitroso-group is oxidised to a nitro-group with the formation of *p*-nitrodimethylaniline. By boiling nitrosodimethylaniline with alkali, the $\text{—N(CH}_3)_2$ group is split off, with the production of nitrosophenol (235) and dimethylamine (47), which can be prepared in a pure state in this way:

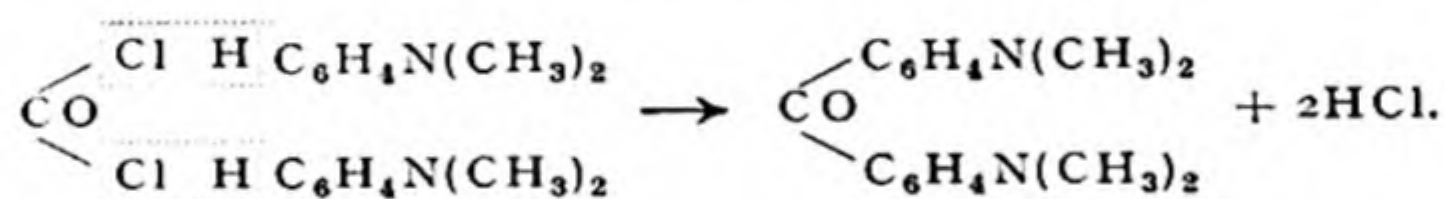


The *para*-hydrogen atom in dimethylaniline can also react with aldehydes with the formation of a condensation product:

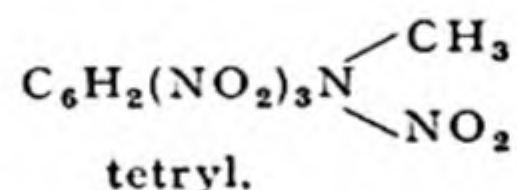


The structure of this compound follows from its relationship to triphenylmethane $\text{CH(C}_6\text{H}_5)_3$ (273).

A *para*-substituted derivative of *benzophenone* (259) called *Michler's ketone*, which is an intermediate product in the preparation of certain dyestuffs, is produced from phosgene and dimethylaniline:



When dimethylaniline is warmed with fuming nitric acid, *trinitrophenylmethylnitramine* is formed with the evolution of a large amount of gas (VAN ROMBURGH):



One of the methyl groups is oxidised away and replaced by a nitro-group and, at the same time, hydrogen atoms in positions 2, 4 and 6 in the nucleus, are also replaced by NO_2 . This substance is used as an explosive under the name of *tetryl*. The same reaction takes place with other dialkylanilines.

Quaternary bases are produced by adding alkyl halides to tertiary mixed amines and treating the resultant quaternary salts with moist silver oxide. These compounds behave like strong bases.

On boiling dimethylaniline methiodide with potash, methyl alcohol and dimethylaniline are produced; thus the reaction takes a different course to that which occurs when quaternary aliphatic ammonium bases are heated (49).

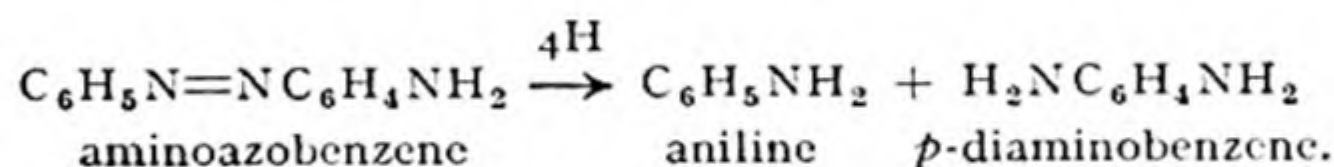
Phenylphosphine, $\text{C}_6\text{H}_5\text{PH}_2$, the phosphorus compound corresponding with aniline in structure, is obtained by distilling *phenylphosphinodichloride*, $\text{C}_6\text{H}_5\text{PCl}_2$, with alcohol

in a stream of carbon dioxide; in this reaction the alcohol acts as a reducing agent. It is a liquid with a nauseating odour; it is very easily oxidised. Phenylphosphinodichloride, which serves as the starting product for many aromatic phosphorus compounds, is prepared by warming benzene with phosphorus trichloride and aluminium chloride.

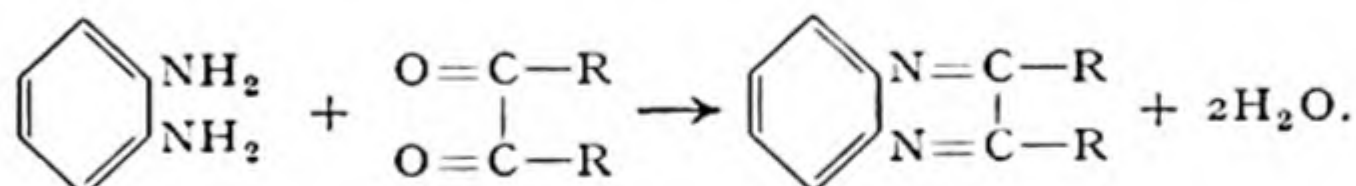
238. *Poly-amino-compounds* are obtained by reduction of poly-nitro-compounds. Diamines are also produced from dichlorobenzenes or chloroanilines by heating with aqueous ammonia to 140–200° with copper sulphate as a catalyst. The di- and tri-aminobenzenes are easily oxidised like the polyhydric phenols; they are colourless when pure but rapidly darken when exposed to the atmosphere.

The *diaminobenzenes*, which are also called *phenylenediamines* (*phenylene* is the name for the radical derived from benzene by removing two atoms of hydrogen, *i.e.* C₆H₄), are solid substances used in the manufacture of dyestuffs. They are fairly soluble in water and may be distilled without decomposition.

p-Diaminobenzene can be obtained from aminoazobenzene (249) by reduction with tin and hydrochloric acid:



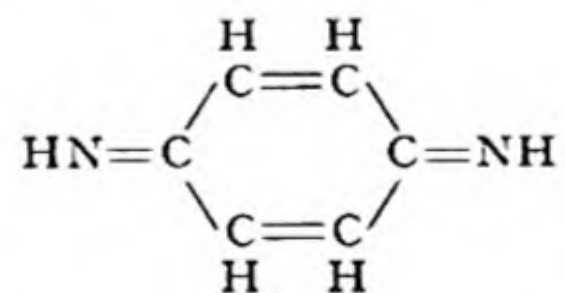
o-Diaminobenzene reacts readily with 1,2-diketones (especially with phenanthraquinone 284) with the formation of *quinoxalines* (343):



m-Diaminobenzene gives an intense brown colour in aqueous solution with even very dilute nitrous acid.

p-Diaminobenzene gives quinone (235) on oxidation.

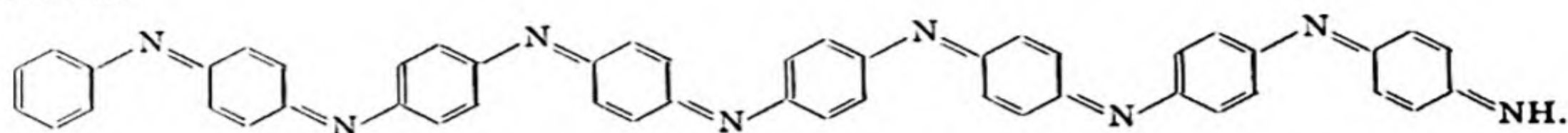
Oxidation of this diamine with silver oxide gives *quinonediimine*:



which is split up into quinone and ammonia by the action of dilute acids.

Aniline-black. On oxidising aniline in acid solution, *e.g.* with potassium chlorate or bichromate, various insoluble, green to black colouring matters are produced, the exact composition depending on the oxidising agent employed; these form the constituents of *aniline-black*. The ultimate product of oxidation at low temperatures

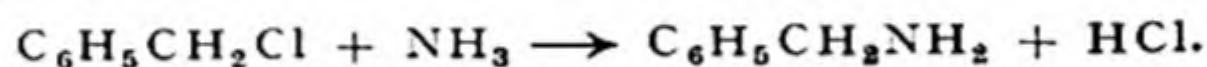
is pernigraniline, which should have the following structure according to WILL-STÄTTER:



In this formula there are eight aniline residues joined together through nitrogen and there are four quinonoid groupings in the molecule. In support of this formula, a good yield of quinone is produced from aniline-black by oxidation. Aniline-black, obtained commercially by oxidising aniline at a higher temperature, which is stable towards acids, is probably produced by a reaction between pernigraniline and aniline, in which hydrogen is removed by oxidation (GREEN). Aniline-black is one of the most important dyestuffs for dyeing cotton. In this process cotton is steeped in an acid solution of aniline salt (hydrochloride) and then treated with a solution of sodium bichromate to which a copper salt is added, as a result of which the dyestuff is produced directly on the fibre.

Amines with the amino-group in the side-chain.

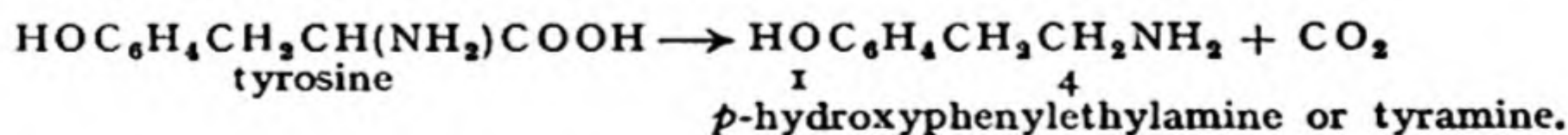
239. *Phenylaminomethane* or *benzylamine* $C_6H_5CH_2NH_2$, is the simplest compound of this group. It is isomeric with the toluidines but resembles the aliphatic amines in properties, which is evident also in its method of formation from benzyl chloride and ammonia (in which di- and tri-benzylamines are also produced):



It is also formed by addition of hydrogen to benzonitrile and by reduction of phenylnitromethane $C_6H_5CH_2NO_2$ (226). It is a liquid boiling at 185° , which reacts alkaline in water and does not give a diazonium compound (245). It is a stronger base than aniline because the amino-group is situated in the side-chain and is not under the direct influence of the phenyl group. Benzylamine derivatives alkylated in the amino-group, *e.g.* $C_6H_5CH_2NHR$ ($R = CH_3, C_2H_5$, etc.) are much more strongly basic than benzylamine.

β -Phenylethylamine or 1-amino-2-phenylethane $C_6H_5CH_2CH_2NH_2$, is a decomposition product of proteins; it originates from phenylalanine (199). Various bases occurring in plants or animals, such as *tyramine*, *hordenine*, *adrenaline* and *ephedrine*, are derived from phenylethylamine. These compounds contain phenolic hydroxyl groups.

Tyramine is produced in the decomposition of proteins by bacteria and also occurs in ergot. Its structure follows from its formation from tyrosine (199), from which it is obtained by heating with the elimination of carbon dioxide:

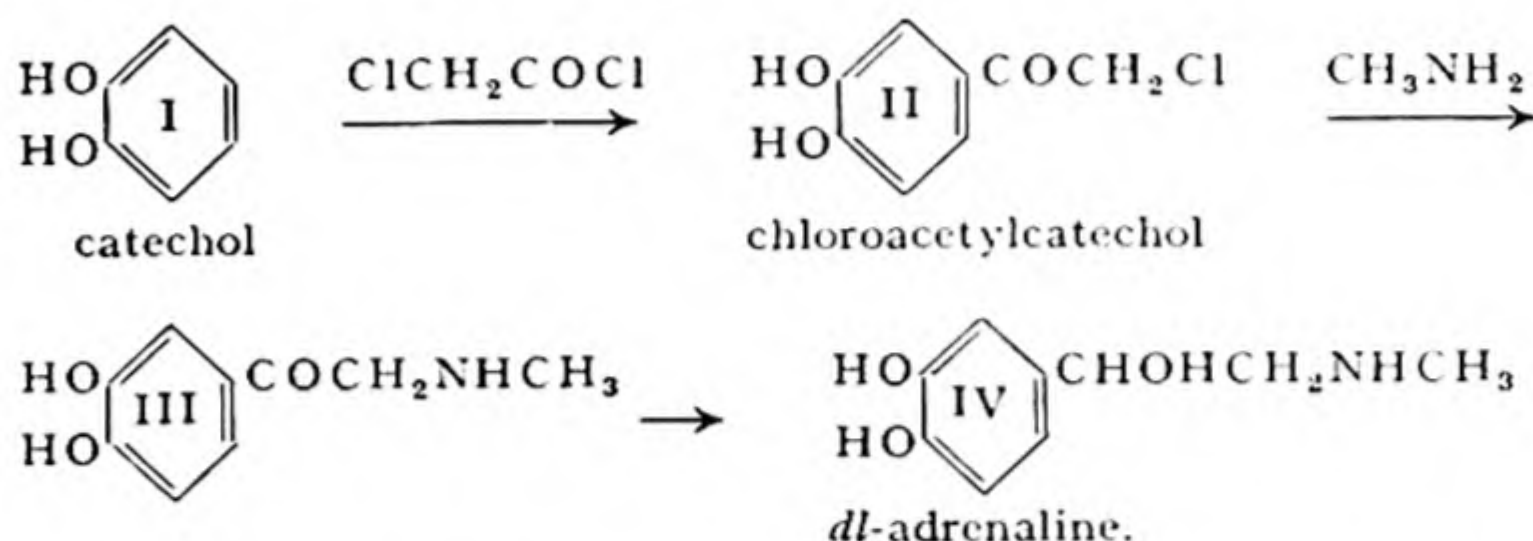


Tyramine is used in medicine; it causes contraction of the peripheral blood vessels and a rise in the blood pressure.

Adrenaline is a hormone (307) occurring in the suprarenal gland. It can be isolated from the suprarenal glands of horses and is used in medicine because it brings about

constriction of the blood vessels. Protocatechuic acid (263) is formed when adrenaline is oxidised; methylamine is split off on heating with hydriodic acid. Also, it may be shown by benzylation and acetylation, that adrenaline contains an alcoholic hydroxyl group. The structural formula deduced from these data has been confirmed by the following synthesis (STOLZ).

By the action of chloroacetyl chloride on catechol (I), chloroacetylcatechol (II) is formed, which reacts with methylamine to give the amino-ketone (III); on reduction, *e.g.* with sodium amalgam, *dl*-adrenaline (IV) is produced, which can be resolved into its optical components via the tartrates:



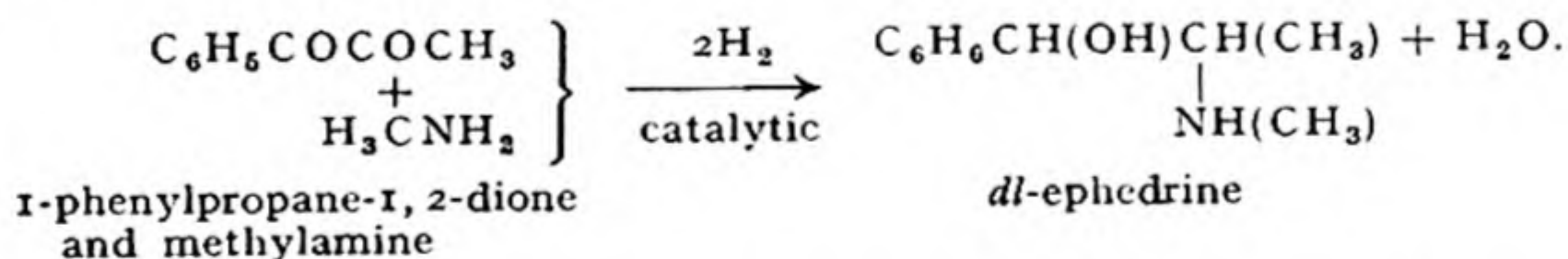
Natural adrenaline is laevo-rotatory, $\alpha_D = -50.5^\circ$.

Hordenine $\text{HO} \begin{array}{c} \diagup \\ \text{ } \\ \diagdown \end{array} \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, melting point 118° , occurs in germinating barley.

Amongst the derivatives of phenylethylamine are the following alkaloids (352).

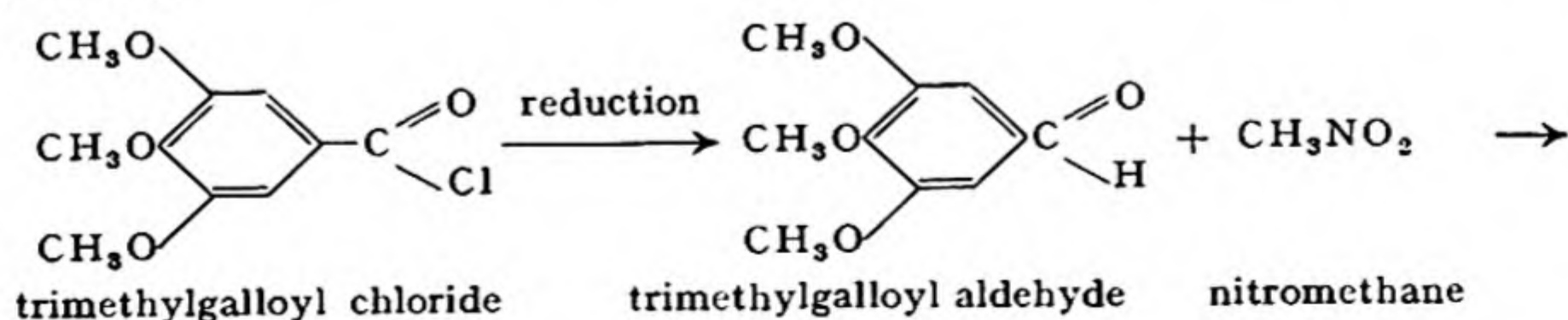
Ephedrine, $\text{C}_{10}\text{H}_{15}\text{ON}$ (crystals which melt at 38° when anhydrous) and the stereoisomer, pseudo- or ψ -ephedrine, occur along with alkaloids of related structure in *Ephedra sinica* and they can be obtained from this source.

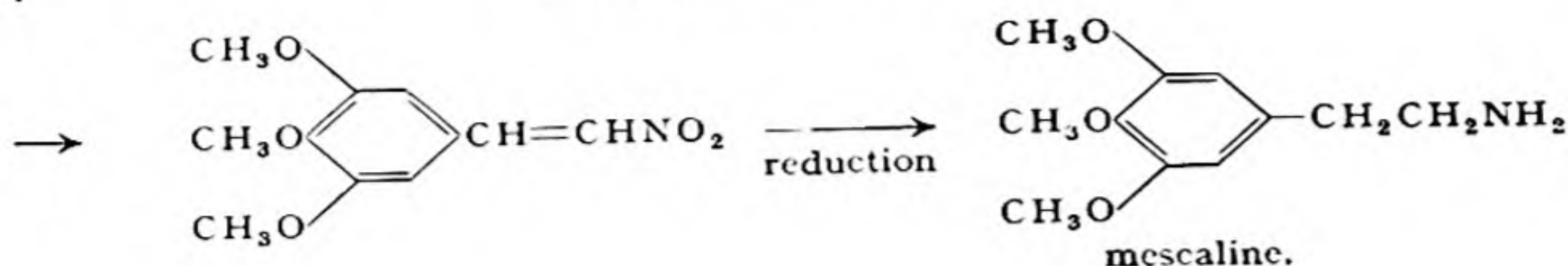
When ephedrine is heated with hydrochloric acid, methylamine is split off. It gives a nitroso-compound. From this it follows that ephedrine is a secondary amine in which a methyl group is attached to the nitrogen. It has an alcoholic hydroxyl group as can be shown by benzylation and it gives benzoic acid on oxidation. These and other data lead to the structure given below, which has been confirmed by synthesis (MANSKE and JOHNSON; SKITA):



Ephedrine causes an increase in the blood pressure and is used in medicine.

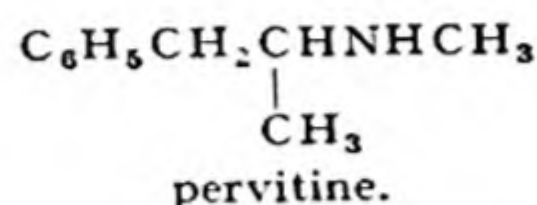
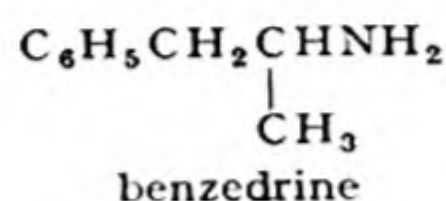
Various alkaloids occur in certain species of cacti, *e.g.* *Anholium*, which are indigenous to Mexico. One of these, *mescaline* $\text{C}_{11}\text{H}_{17}\text{O}_3\text{N}$, a colourless liquid boiling at 180° at 12 mms. pressure, is a derivative of phenylethylamine as appears from the following synthesis (SPÄTH):





In man, mescaline causes peculiar colour vision.

Some non-oxygenated derivatives of β -phenylethylamine show remarkable pharmacological properties, e.g. α -methyl- β -phenylethylamine (*benzedrine*) and its N-methyl derivative (*pervitine*):



These substances exert a powerful stimulating action and excite the activity of the central nervous system. These bases are cardiac and nervous stimulants.

Nuclear substituted anilines.

240. Halogen substitution products. In general bromine and chlorine react violently with aromatic amines. In order to introduce one chlorine atom into aniline, the starting material must be acetanilide, which is dissolved in glacial acetic acid and gaseous chlorine is passed into the solution. The main product is *p*-chloroacetanilide.

In this reaction the hydrogen atom attached to the nitrogen is first substituted; this compound, N-chloroacetanilide, passes over into *p*-chloroacetanilide by an intramolecular conversion (BLANKSMA).

By the continued action of chlorine the acetyl compounds of 2,4-dichloro- and finally of 2,4,6-trichloro-aniline are produced. For 2,4,6-tribromoaniline see 236.

o- and *m*-Halogenoanilines are obtained by reduction of the corresponding nitrohalogenobenzenes (225). The basic properties of aniline are weakened by introducing halogen atoms in the *o*- and *p*-positions in the nucleus; a halogen atom in the *m*-position has very little effect.

Nitro-compounds of aromatic amines or nitranilines $\text{C}_6\text{H}_4(\text{NO}_2)(\text{NH}_2)$ are produced from dinitro-compounds by partial reduction with ammonium sulphide. A second method of preparation consists of nitrating the aromatic amine. However, if nitric acid is allowed to react with free aniline, the latter is mainly oxidised. The amino-group must be protected from the oxidising action of nitric acid by introducing an acyl residue, e.g. acetyl. In the nitration of acetanilide, *p*-nitroacetanilide is the main product together with a little *o*-nitroacetanilide. *p*-Nitraniline (m.p. 147°) and *o*-nitraniline (m.p. 71°) are obtained by boiling the nitroacetanilides with hydrochloric acid.

Aniline can also be nitrated by allowing nitric acid to react on the sulphate in concentrated sulphuric acid. For this purpose aniline is dissolved in excess sulphuric acid; *p*- and *m*-nitraniline (m.p. 114°) are formed in approximately equal quantities along with a little *o*-nitraniline.

Hence substitution in the *meta*-position is facilitated by converting aniline into the anilinium ion $C_6H_5NH_3^+$.

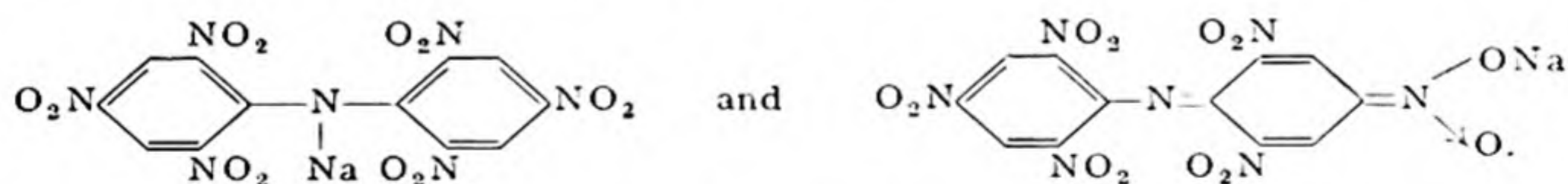
For the formation of amines from chloro- and bromo-nitrobenzenes, see 225.

The basic character of the nitranilines is weakened when compared with aniline, most with the *ortho*- and least with the *meta*-isomer; *o*-nitraniline sulphate is almost completely hydrolysed by water, while that of *m*-nitraniline is very slightly hydrolysed. The nitranilines are yellow, crystalline compounds, which are sparingly soluble in water and readily soluble in alcohol.

The amino-group in *o*- and *p*-nitraniline, but not in *m*-nitraniline can be replaced by a hydroxyl group by heating with potash; the potassium salts of the nitrophenols (235) are produced.

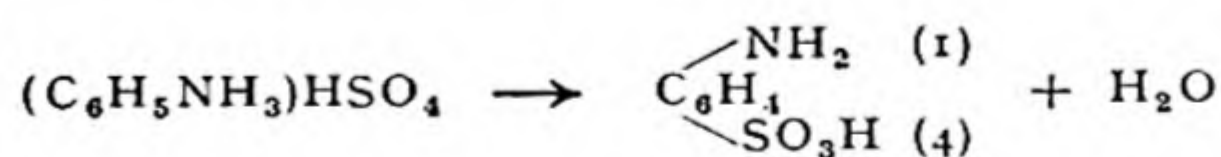
The amino-group in *picramine*, 2,4,6-trinitraniline, is very easily replaced by hydroxyl.

Nitro-compounds of diphenylamine. The most important compound of this group is *hexanitrodiphenylamine*, produced by the nitration of diphenylamine. This substance can form alkali salts in which an atom of hydrogen is replaced by a metal atom. These salts may be represented by two tautomeric formulæ:

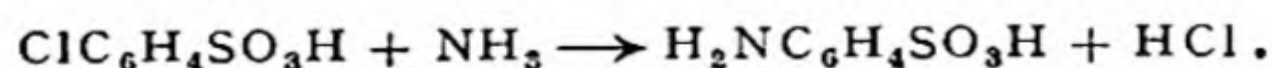


Salts are known which occur in red and yellow forms. The sodium and ammonium salt was used under the name *aurantia*, as a yellow dyestuff for silk and leather and as a light filter for photographic purposes.

241. Sulphonic acids of aromatic amines. Of these *p*-aminobenzenesulphonic acid or *sulphanilic acid*, $C_6H_4(NH_2)(SO_3H)$, will be mentioned. It is produced by heating aniline sulphate to 200°:



or by heating *p*-chlorobenzenesulphonic acid with ammonia to 200° in presence of copper sulphate as a catalyst:



Sulphanilic acid decomposes without melting at 300° and is insoluble in

organic solvents. It must therefore be regarded as an amphoteric ion $\text{H}_4\text{C}_6\begin{smallmatrix} \text{SO}_3^- \\ \text{NH}_3^+ \end{smallmatrix}$. It can give salts with alkalis, e.g. $\text{H}_4\text{C}_6\begin{smallmatrix} \text{SO}_3\text{Na} \\ \text{NH}_2 \end{smallmatrix}$. It crystallises with two molecules of water of crystallisation and is sparingly soluble in cold water; it is used as an intermediate in the dyestuffs industry.

The amide of sulphanilic acid, *sulphanilamide*, $\text{H}_2\text{NC}_6\text{H}_4\text{SO}_2\text{NH}_2$, hinders the multiplication of streptococci. Many derivatives of this compound possess the property of preventing the growth of bacteria and are used as drugs against infectious diseases (antibiotics see 254, 335).

On fusing sulphanilic acid with potash, the reaction product is not aminophenol as would be expected, but aniline. Quinone is formed on oxidation with chromic acid.

Hydroxy-compounds of aromatic amines or *aminophenols* $\text{C}_6\text{H}_4(\text{OH})(\text{NH}_2)$, are produced by reducing nitrophenols (235). The aminophenols have no acidic characteristics; they do not give phenates; they form salts with acids. The aminophenols form colourless leaflets, which are soon oxidised in the air with the production of a brown colour and resinous material; the hydrochlorides are more stable.

p-Aminophenol can be prepared by the electrolytic reduction of nitrobenzene in acid solution, phenylhydroxylamine being formed as the initial reaction product (see 244).

An alkaline solution of *p*-aminophenol rapidly becomes dark in colour when exposed to air; it is stable, however, if sodium sulphite is also present. Such a solution is a good photographic developer.

LUMIÈRE has discovered some general rules, which must be fulfilled by aromatic compounds if they are to be of use as photographic developers. He has shown, for example, that such compounds must contain more than one hydroxyl or amino-groups, or at least one amino- and one hydroxyl group. Hydroquinone, pyrogallol and *metol* or *p-methyl-aminophenol* $\text{HOC}_6\text{H}_4(\text{NHCH}_3)$, are photographic developers, which fulfil these requirements.

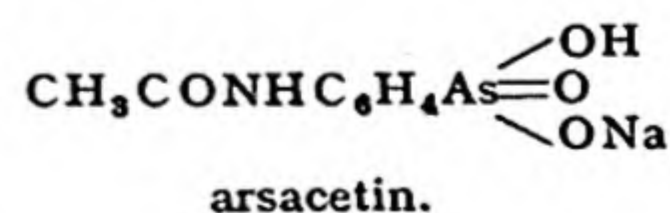
A derivative of *p*-aminophenol, *acetylphenetidine*, $\text{C}_6\text{H}_4(\text{OC}_2\text{H}_5)(\text{NHCOCH}_3)$ -1,4, is used as a febrifuge under the name of *phenacetine*.

242. Arsenic compounds of aniline. *p-Aminophenylarsonic acid* (*arsanilic acid*) $\text{H}_2\text{NC}_6\text{H}_4\text{AsO}(\text{OH})_2$, is produced in a similar way to sulphanilic acid by heating aniline arsenate $(\text{C}_6\text{H}_5\text{NH}_2)_2\text{H}_2\text{AsO}_3$.

Aminophenylarsonic acid can be diazotised, showing the presence of a free amino-group. *p*-Iodoaniline is produced by the action of iodine with elimination of the arsenic acid residue. From this it follows that the above formula is correct.

Various aromatic arsenic compounds are used in medicine for combatting infectious diseases caused by spirochaetae and trypanosomes.

The sodium salt of aminophenylarsonic acid, known under the name of *atoxyl*, and to a larger extent, the sodium salt of the acetyl compound *arsacetin*, are used in the treatment of sleeping-sickness.

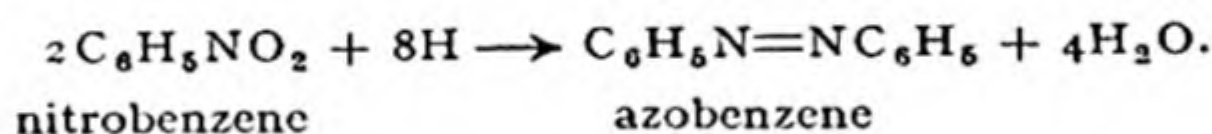


On the basis of this isomerism, which is also observed with other mono-substituted azoxybenzenes, the above formulae are attributed to azoxy-compounds instead of the formula $\text{C}_6\text{H}_5\text{N}=\text{N}(\text{O})\text{C}_6\text{H}_5$, in use previously; the bond between nitrogen and oxygen is a semi-polar bond. Azobenzene is produced on warming azoxybenzene with iron powder.

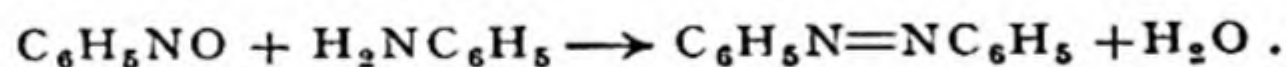
Azoxybenzene is converted into *p*-hydroxyazobenzene $\text{C}_6\text{H}_5\text{N}=\text{NC}_6\text{H}_4\text{OH}$, by warming with concentrated sulphuric acid. A similar reaction takes place when the azoxy-compound is irradiated but the *ortho*-compound is produced.

p-Azoxyphenetole $\text{C}_2\text{H}_5\text{OC}_6\text{H}_4\text{N}=\text{N}(\text{O})\text{C}_6\text{H}_4\text{OC}_2\text{H}_5$, melts at 134° to a turbid liquid, which goes suddenly clear at 165° . When the turbid liquid is viewed between crossed nichols in convergent light, interference figures are observed, which are characteristic for double-refracting uniaxial crystals. Between 134° and 165° the fused melt is anisotropic but above 165° , the anisotropy disappears; these anisotropic liquids are called *liquid crystals* or *crystalline liquids*. This phenomenon, which has been particularly investigated by LEHMANN and by VORLÄNDER, occurs in a large number of compounds having elongated molecules. It is supposed that groups of molecules orientated in parallel occur in crystalline liquids and so give rise to anisotropy.

Azobenzenes are produced by reduction of nitro-compounds with iron powder or zinc dust and alkali or with stannous chloride in excess alkali or with sodium amalgam and dilute alcohol. In this way *azobenzene*, the simplest compound of this group, can be prepared from nitrobenzene:

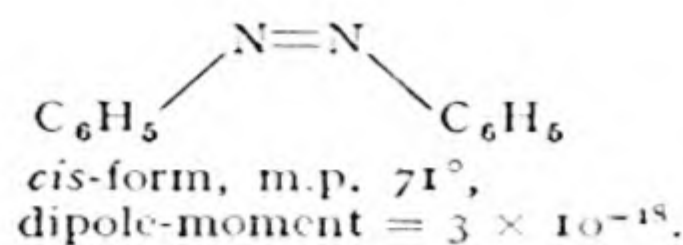
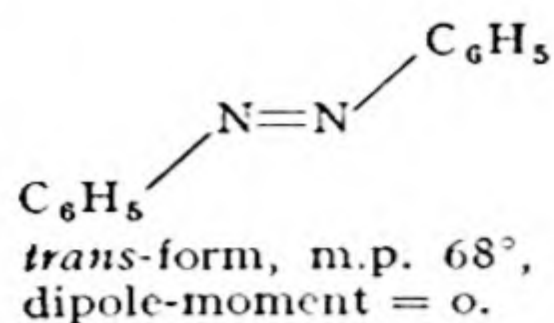


Condensation to azo-compounds occurs on boiling equimolecular quantities of aromatic primary amines and nitroso-compounds in glacial acetic acid:



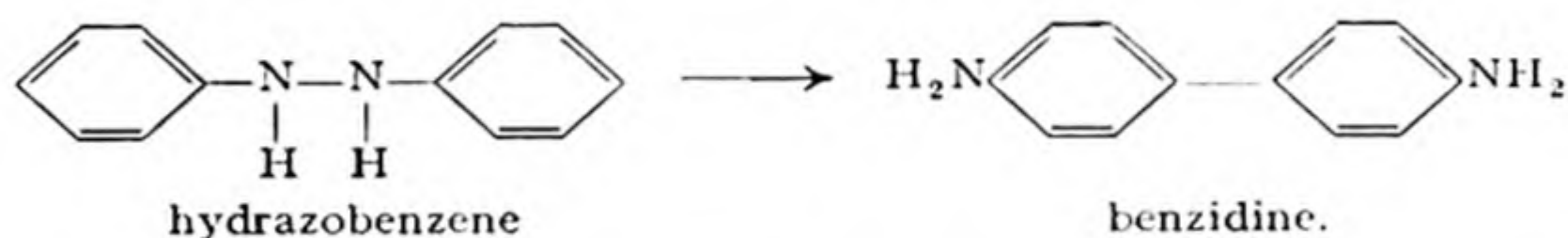
Azobenzene is also produced along with azoxybenzene by oxidising aniline with potassium permanganate. Azobenzene is insoluble in water and can be distilled without decomposition. It is a reddish orange, crystalline substance boiling at 295° and melting at 68° . Its structure follows from its reduction to aniline.

The azobenzene molecule can be represented by two stereoisomeric *cis* and *trans*-forms, the phenyl groups lying on the same side or on opposite sides, of the plane containing the double bond between the nitrogen atoms. Actually two isomeric forms of azobenzene, melting respectively at 68° and 71° , have been discovered (G. S. HARTLEY). The modification melting at 69° has zero dipole-moment (79), from which it follows that the molecule has a centre of symmetry; therefore the *trans*-configuration is ascribed to this form.



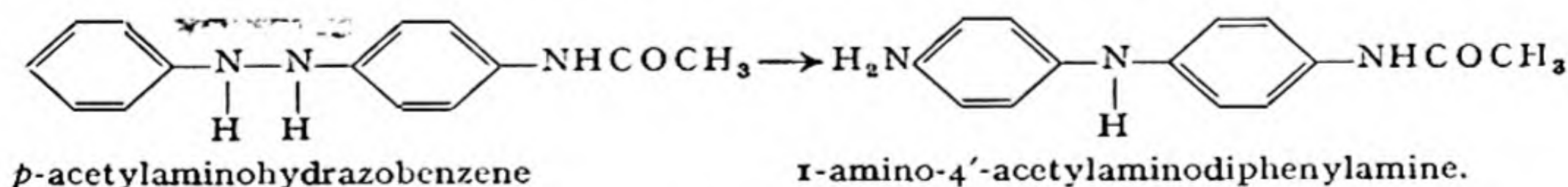
By irradiation in solution, the *trans*-form is partly converted into the modification melting at 71° ; this form has a dipole-moment of 3×10^{-18} and possesses the *cis*-configuration. On warming in the dark, the *cis*-form passes over into the more stable *trans*-form. *Cis*- and *trans*-isomerism has been observed with several derivatives of azobenzene and in these cases also the *trans*-form is the stable modification.

Hydrazobenzene $\text{C}_6\text{H}_5\text{NHNHC}_6\text{H}_5$, is produced by boiling nitrobenzene or azobenzene with zinc dust in alcoholic potash. It is a colourless compound melting at 126° . On further reduction it is converted into aniline; azobenzene is readily obtained from it by oxidation, *e.g.* with ferric chloride. This oxidation takes place slowly when the substance is exposed to air. A characteristic reaction for hydrazobenzene is its conversion into *benzidine* or *4,4'-diaminodiphenyl*:



This reaction takes place when hydrazobenzene is treated with strong acids. By replacing the amino-groups in benzidine by hydrogen (see 246), diphenyl (273) is obtained, hence benzidine is a diphenyl-derivative. Benzidine is also produced by reducing azobenzene in acid solution; benzidine sulphate is very sparingly soluble in cold water. When the hydrogen atoms in the *para*-positions in hydrazobenzene are substituted, the latter cannot be converted into a benzidine derivative. From this it follows that the amino-groups in benzidine occupy the *para*-positions.

In some cases, hydrazo-compounds with only one of the *para*-positions substituted, can undergo an intramolecular transformation, which is known as a *half benzidine* or *semidine transformation*. This reaction produces derivatives of *diphenylamine*:



The mechanism of the benzidine transformation is not yet completely elucidated.

Electrolytic reduction, especially of nitro-compounds

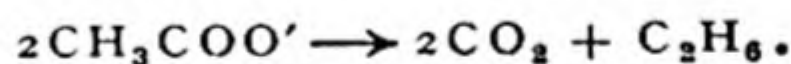
244. In the electrolysis of an acid solution, in which the concentration of hydrogen-ions is 1-normal, the hydrogen-ions are discharged if a definite

potential difference is maintained between the electrolyte and the cathode. When using a platinum electrode, this potential difference agrees, for practical purpose, with the equilibrium potential of a normal hydrogen electrode. This potential, which serves as the zero-point for potential measurements, is given the value $E=0$. If, however, a lead or mercury cathode is employed, then the hydrogen-ions are discharged only when the potential difference between electrolyte and cathode is very much more negative than the zero value; in this case the potential value may even exceed 1 volt. This phenomenon is called *overvoltage*; thus a considerable overvoltage can be maintained at such electrodes. Experience has shown that difficultly reduceable substances, which cannot be reduced at a platinum electrode, can frequently be reduced at a cathode at which an overvoltage can be maintained.

Thus by suitable choice of the cathode material, in some cases it is possible to carry out reductions electrolytically which would not be possible by other means.

A second factor which may be of importance in electrolytic processes, is the *current density*. By this is meant the strength of the current in amperes divided by the surface area of the electrode in cm^2 . The number of ions discharged per unit time and unit of surface area of the electrode, is therefore proportional to the current density.

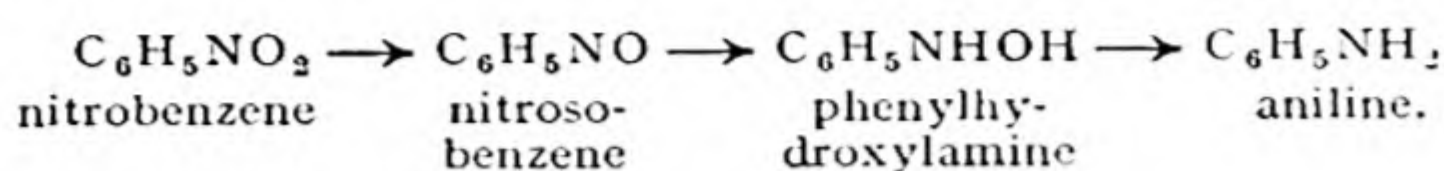
In reactions in which the discharged ions must react with one another, it is important to work at a high current density, which is attained by arranging for the electrode at which the reaction takes place, to have a small surface area. In this way the concentration of discharged ions in the immediate neighbourhood of the electrode is indeed high. An example is the formation of ethane by the electrolysis of acetic acid as described by KOLBE; in this case the anions react at the anode according to the equation:



In the contrary case, in electrolytic reductions in which the hydrogen-ions discharged at the cathode must react with the substance dissolved in the solution, it is important that the cathode surface in contact with the liquid should be large; hence in this case a large cathode surface and a low current density are used. If it is desired to work at a high overvoltage, however, a high current density is required in order to reach it; a cathode with a small surface is then chosen.

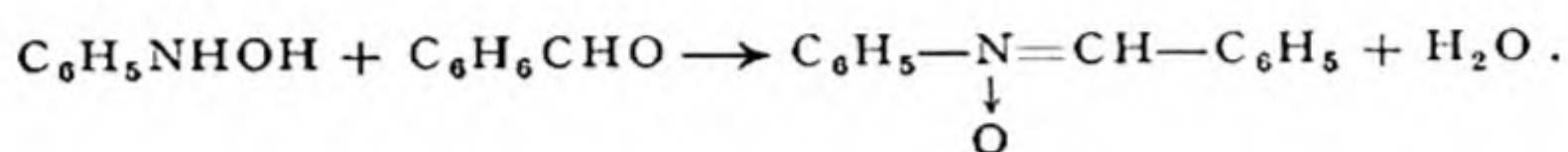
The electrolytic reduction of nitro-compounds is important both from theoretical and practical aspects, because various intermediate products can be obtained before the final product, the corresponding amine, is produced. In the electrolytic reduction of nitrobenzene a distinction must be

drawn between *primary* and *secondary* reduction products. The primary reduction process takes place as follows:



Nitrosobenzene may be produced presumably, from phenyldihydroxylamine $\text{C}_6\text{H}_5\text{N}(\text{OH})_2$, formed initially.

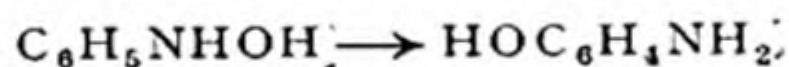
The presence of nitrosobenzene can be demonstrated by adding hydroxylamine to the liquid, when it reacts with the elimination of water and the production of benzenediazonium hydroxide $\text{C}_6\text{H}_5\text{N}_2\text{OH}$, which can be coupled subsequently with α -naphthol giving an azo-dyestuff; *phenylhydroxylamine* can be detected by allowing it to condense with benzaldehyde to give *benzalphenylhydroxylamine*:



Nitrosobenzene can also be prepared by reducing nitrobenzene with zinc dust and water or by the oxidation of aniline with persulphuric acid (H_2SO_5).

When nitrobenzene is reduced in dilute sulphuric acid solution (alcohol being added to dissolve the nitrobenzene, which is only very slightly soluble in dilute sulphuric acid), at a lead cathode with the current strength so chosen that the reduction takes place rapidly, aniline is obtained in a yield of about 90 % of the theoretical.

If the solution is strongly acid, however, the phenylhydroxylamine is rapidly converted into *p*-aminophenol, which cannot be reduced further:

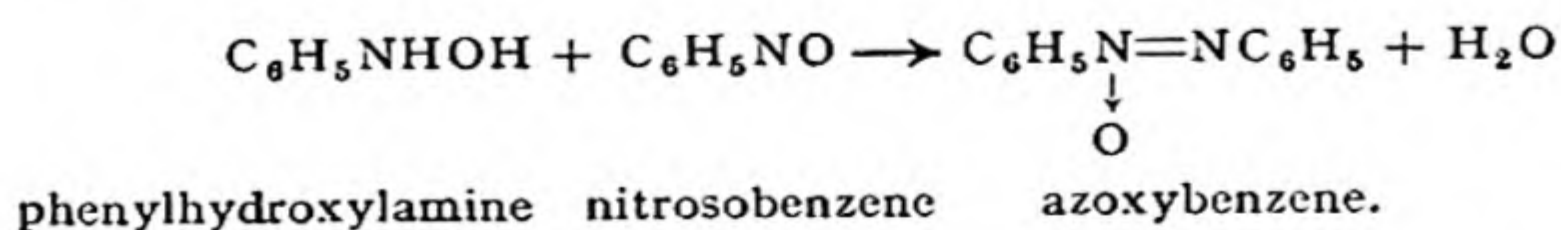


consequently, even in dilute acid solution the theoretical yield of aniline is not obtained, since some of the phenylhydroxylamine formed as an intermediate will be transformed into aminophenol.

For the preparation of phenylhydroxylamine the reduction is carried out in acid solution to which sodium acetate has been added to reduce the hydrogen-ion concentration and a platinum or nickel cathode is used. At the potential maintained by this cathode, the phenylhydroxylamine is not reduced further.

Two other secondary reactions occur in alkaline solution:

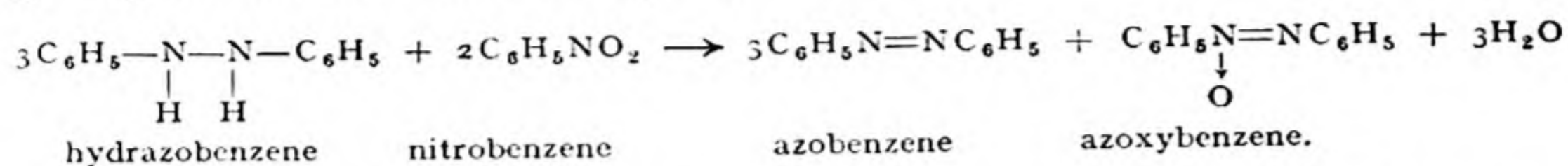
1. Azoxybenzene (243) is produced by the action of phenylhydroxylamine on nitrosobenzene:



In the presence of alkali, this reaction takes place much more rapidly than

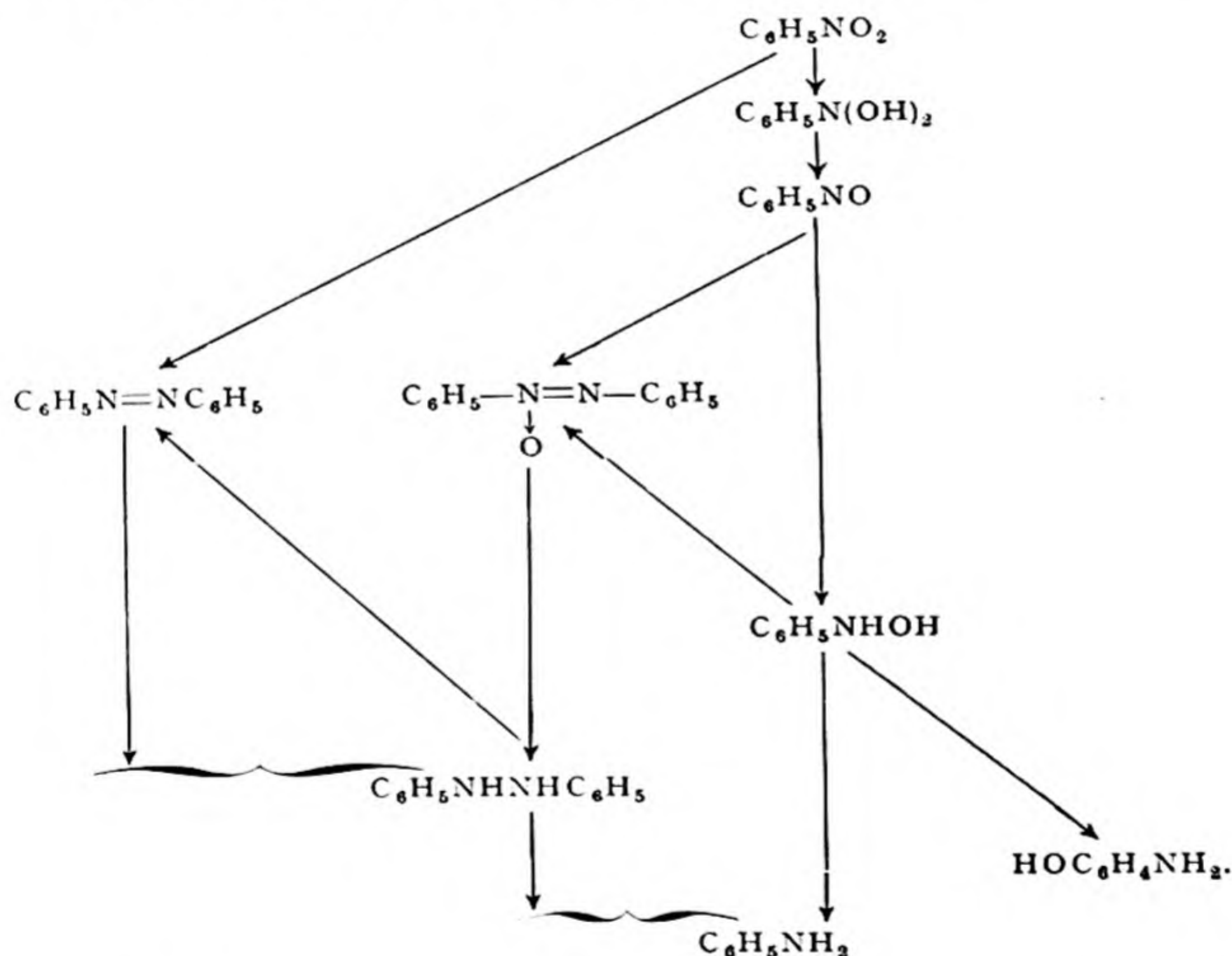
the reduction of phenylhydroxylamine to aniline, so that the latter is produced only in very small amounts. On the other hand, further reduction products of azoxybenzene, particularly hydrazobenzene, are formed.

2. Hydrazobenzene rapidly reacts with any nitrobenzene still present, giving azobenzene and azoxybenzene:



Further, hydrazobenzene is converted very easily into azobenzene by the action of atmospheric oxygen, so that excellent yields of azobenzene can be obtained.

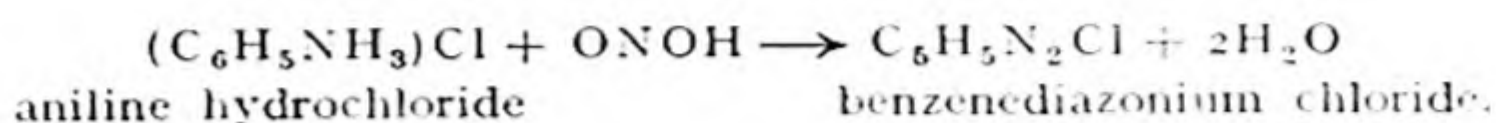
Reduction of hydrazobenzene to aniline occurs at a cathode potential which is about 0.5 volt more negative than the potential at which phenylhydroxylamine is produced; even then the formation of aniline is very slow. Consequently hydrazobenzene can be obtained as the final product from electrolytic reduction in an alkaline medium.



In the reaction scheme (HABER) given above, the vertical arrows show the primary electrolytic reductions and the slanting arrows the secondary processes.

(ix) DIAZONIUM, DIAZO- AND AZO-COMPOUNDS

245. *Diazonium compounds*, which were discovered by GRIESS (1860), are produced by the action of nitrous acid on the salts of primary aromatic amines, *e.g.*:



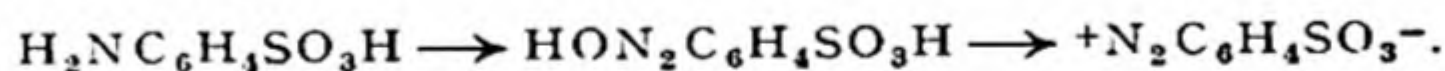
The diazonium compounds are of very great importance; they are employed as intermediate products in the preparation of many benzene derivatives and azo-dyestuffs. "Diazotisation" is carried out as follows:

1 Mol. of aniline salt is dissolved in mineral acid, which must be present in excess (at least 2-2.5 equivalents). To this solution is then added drop by drop with stirring and cooling, a concentrated aqueous solution of 1 mol. of sodium nitrite. Since the diazonium salts decompose easily, the temperature of the reaction mixture must be kept at about 0°. The reaction takes a bimolecular course and is exothermic; the reaction velocity increases on the addition of an excess of strong acid.

The simple diazonium salts are colourless, crystalline compounds, which are readily soluble in water, sparingly soluble in alcohol and glacial acetic acid and insoluble in ether. As a rule they are not isolated in the solid state, because many of them are then extremely explosive and also because the aqueous solution may be used for conversion into other products.

If it is desired, for example, to isolate benzenediazonium nitrate, in the solid form, aniline is dissolved in dilute nitric acid and nitrous gases are passed into the solution. The diazonium nitrate separates out in the crystalline form on adding alcohol and ether.

An example of a diazonium salt, which is difficultly soluble in water, is the "internal salt" of *benzenediazoniumsulphonic acid*, which is produced by introducing a mixture of aqueous solutions of sulphanilic acid (**241**) and sodium nitrite into dilute sulphuric acid. This compound, which is relatively stable, must be considered as an amphoteric ion. (Compare *betaine*, **195**):

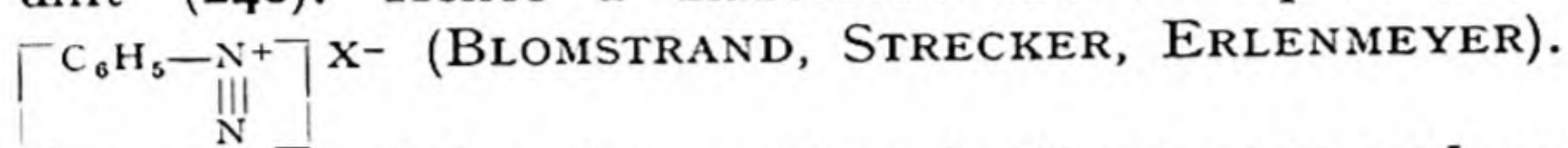


This compound is important for the preparation of azo-dyestuffs (see helianthin **255**).

Diazonium compounds are decomposed by light. Use is made of this fact in the manufacture of light-sensitive paper, in which the sensitive layer contains, for example, diazonaphtholsulphonic acid and a phenol. After exposure to light, the paper is developed by treatment with moist air containing ammonia. As a result of the alkaline reaction, undecomposed diazo-compound couples with the phenol; thus the unexposed portions are coloured.

Structure of diazonium compounds. They have the character of salts and are similar to ammonium and alkali salts. Aqueous solutions of diazonium chlorides, nitrates and sulphates are strongly ionised, as appears from the

determination of the conductivity; they react neutral. The carbonates react alkaline in solution like alkali carbonates. It follows that the diazonium salts must be ionised according to the scheme $C_6H_5N_2^+$ and Cl^- . Like ammonium salts, diazonium salts also form platinum and gold double salts with the formulae $(C_6H_5N_2Cl)_2PtCl_4$ and $(C_6H_5N_2Cl)AuCl_4$, respectively, as well as perchlorates. It is therefore assumed that a pentavalent nitrogen atom is present in diazonium salts, this being the reason for their basic properties. The grouping N_2 is attached to a carbon atom of the benzene ring with one bonding unit only. This follows from a number of reactions which diazonium compounds undergo, in which the N_2 grouping is replaced by a substituent attached to the benzene nucleus by one bonding unit (246). Hence a diazonium salt is represented by the formula

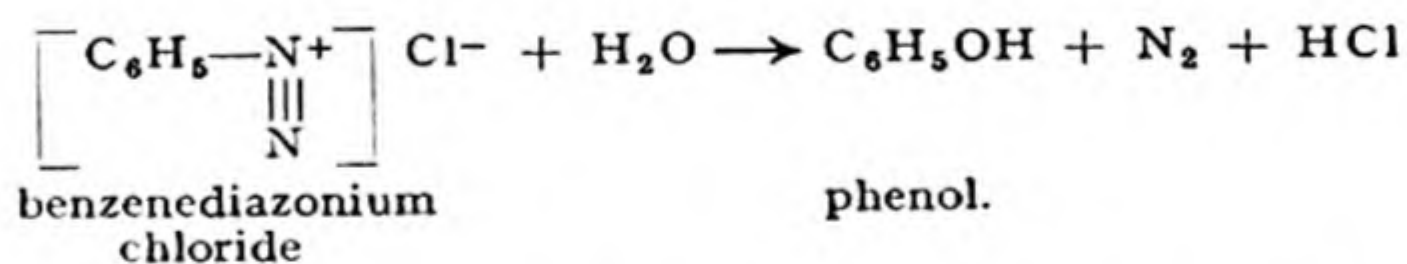


Reactions of diazonium compounds. These compounds can undergo various reactions. In the first group of reactions the nitrogen is replaced by a substituent, which is always attached to the carbon atom to which the diazo group was attached originally. A large number of substitution products of benzene have been prepared via diazonium compounds, because by this means a method is provided for replacing the nitro-group, after reduction and diazotisation, by other substituents.

In the second group of reactions the nitrogen still remains present in the molecule.

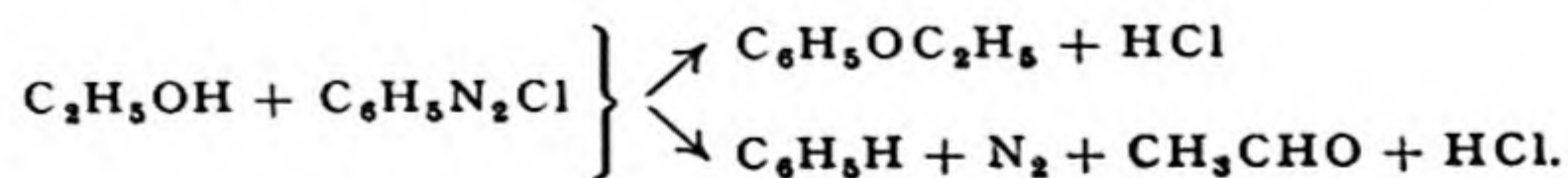
I. Replacement of the group $-N^+ \equiv N$ by a substituent.

246. 1. By *hydroxyl*. When an aqueous solution of a diazonium salt is allowed to stand, or is warmed, evolution of nitrogen takes place and a phenol is formed:

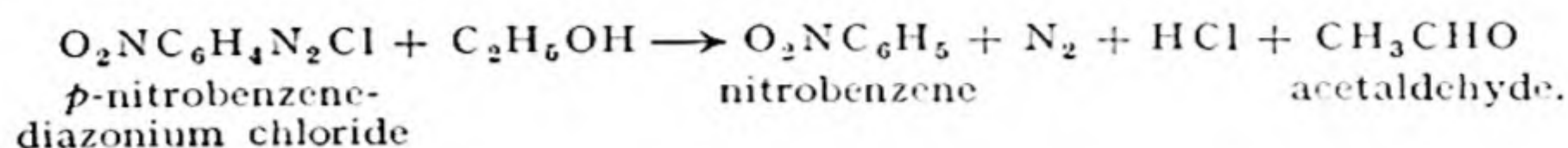


2. By *alkoxyl*, $-OC_nH_{2n+1}$. This happens when an alcoholic solution of a diazonium salt is heated; at the same time, replacement of nitrogen by hydrogen occurs.

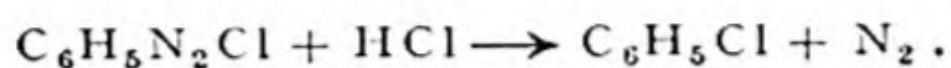
3. By *hydrogen*. This reaction takes place alongside that mentioned under 2; in this case benzene or one of its derivatives is produced, while the alcohol is oxidised to aldehyde:



If the benzene nucleus of the diazonium salt contains nitro-groups or halogen atoms as substituents, then replacement by hydrogen predominates. This is also the case when higher molecular weight alcohols are used:



4. By *chlorine*. When a solution of benzenediazonium chloride is added to a warm solution of cuprous chloride in concentrated hydrochloric acid (SANDMEYER), chlorobenzene is produced:



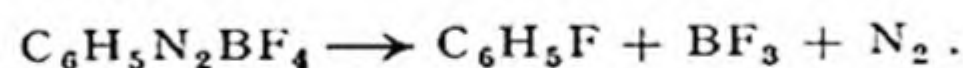
If heating the solution is undesirable, copper powder may be used instead of cuprous chloride according to GATTERMANN.

Cuprous chloride or finely divided copper act catalytically; presumably a cuprous compound is formed as an intermediate.

5. For replacement by *bromine* a solution of potassium bromide is added to an aqueous solution of benzenediazonium sulphate containing free sulphuric acid. On treating this mixture with cuprous bromide or copper powder, bromobenzene is produced with evolution of nitrogen.

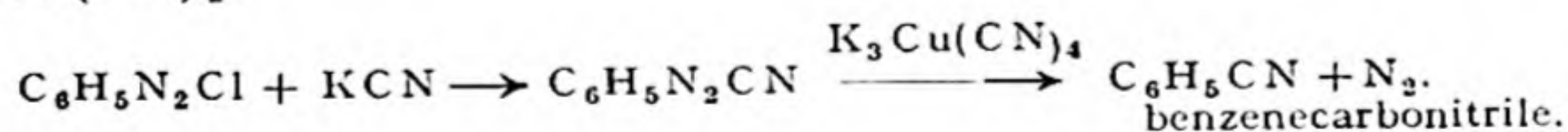
5. By *iodine*. This replacement already takes place when a solution of benzenediazonium sulphate is introduced into a warm solution of potassium iodide.

By *fluorine*. For this purpose a solution of hydrofluoroboric acid (HBF_4) is added to a solution of benzenediazonium chloride. Benzenediazonium borofluoride $\text{C}_6\text{H}_5\text{N}_2\text{BF}_4$ separates as a crystalline compound. This substance is stable at ordinary temperatures but decomposes on warming:



Fluorobenzene and many other aromatic fluoro-compounds can be made in this way (BALTZ and SCHIEMANN).

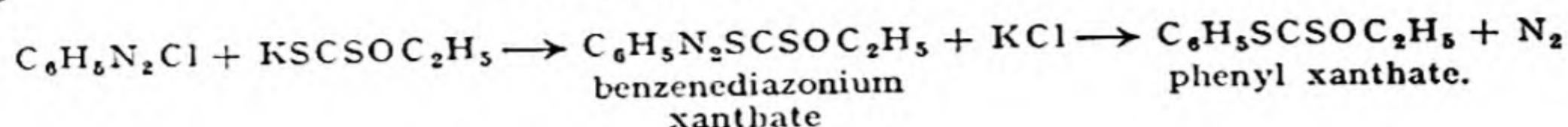
7. By the *carbonitrile group*. According to SANDMEYER's method a solution of the diazonium salt is added to a solution of potassium cuprocyanide, $\text{K}_3\text{Cu}(\text{CN})_4$:



If heating must be dispensed with, copper powder is added to a cold solution of the diazonium salt and potassium cyanide (GATTERMANN).

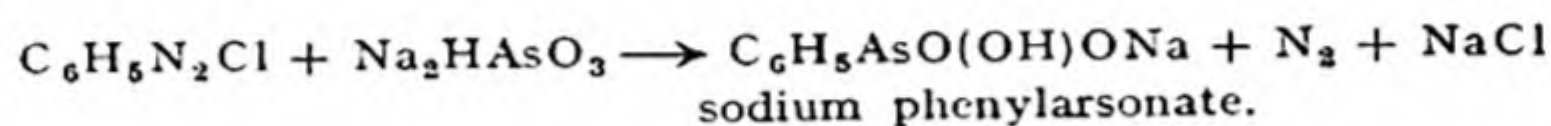
This reaction is of great importance for synthesising aromatic acids, which are produced by hydrolysing the carbonitriles.

8. By a *group containing sulphur*. If a solution of potassium xanthate (154) is added to a solution of a diazonium salt, the diazonium xanthate separates:



On warming the solution, the diazonium xanthate decomposes with the evolution of nitrogen and phenyl xanthate is formed. The structure of this compound follows from the formation of benzenesulphonic acid, which is produced by oxidation of the xanthate. This is an appropriate method for introducing sulfo-groups into benzene derivatives in cases where it is not possible to do so by direct sulphonation.


9. By a group containing arsenic. When di-sodium arsenite and then alkali is added to a solution of a diazonium salt, the sodium salt of an arylarsonic acid (223, 249) is obtained (H. BART):

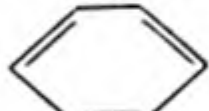



II. Reactions of diazonium-compounds with retention of the nitrogen atoms.

Different kinds of compounds may be formed in this series of reactions:

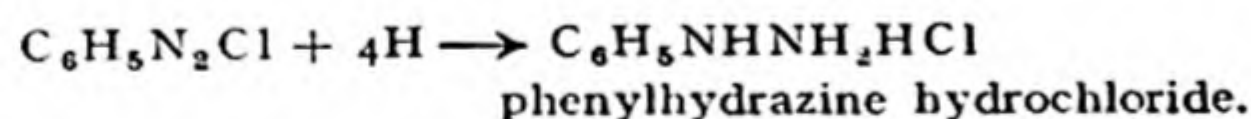
a. hydrazines characterised by the grouping —NH—NH_2 .

b. diazo-compounds  —N=NX , in which X may be an acid residue, an OH-group, or the groupings $\text{—NH—C}_6\text{H}_5$, —OR or —SR .

c. azo-compounds  —N=N—  in which both phenyl nuclei may carry substituents.

247. a. *Aromatic hydrazines* are produced by gentle reduction of diazonium compounds. The most important hydrazine compound is *phenylhydrazine* $\text{C}_6\text{H}_5\text{NHNH}_2$, (E. FISCHER, 1875), which has already been mentioned as a reagent for carbonyl groups in the formation of hydrazones (see 59) and the formation of osazones (see 160).

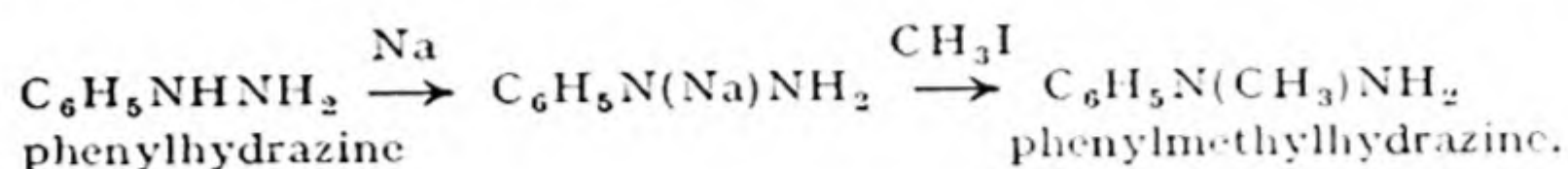
Phenylhydrazine hydrochloride is produced by reduction of benzenediazonium chloride with stannous chloride in hydrochloric acid solution:



It is difficultly soluble in cold water and practically insoluble in concentrated hydrochloric acid. Phenylhydrazine melts at 19.6° to an oily liquid, which darkens in colour in the air; it boils at 241° with slight decomposition; it is poisonous and attacks the skin. Phenylhydrazine is broken down into aniline and ammonia by vigorous reduction and is readily oxidised. Phenylhydrazine sulphate can be oxidised with mercuric oxide to a diazonium salt but to a large extent oxidation goes a stage further with elimination of nitrogen. Phenylhydrazine sulphate is decomposed into benzene, nitrogen

and water by warming with alkaline copper solutions. This is an alternative method for replacing the amino-group by hydrogen (see 246, 3); in this case the amine must first of all be converted into the phenylhydrazine.

In 237 it was mentioned that *methylphenylhydrazine* can be produced by carefully reducing nitrosomethylaniline. This compound can also be obtained from phenylhydrazine by allowing it to react with sodium and then treating the resultant monosodium derivative with methyl iodide:



From this it follows that phenylhydrazine contains an amino-group, which establishes the structure of this compound.

Phenylhydrazine is used in the manufacture of many technically important products, including antipyrine and its derivatives (323) and some important dyestuffs.

Symmetrical diarylhydrazines, e.g. $\text{C}_6\text{H}_5\text{NHNHC}_6\text{H}_5$, are known as hydrazo-compounds (see 243).

248. b. Diazo-compounds. In the same way as ammonium hydroxide is produced from ammonium salts by the action of alkalis, strongly alkaline solutions are produced from diazonium chlorides and silver hydroxide or from diazonium sulphates and the equivalent quantity of barium hydroxide. It is assumed that these solutions contain diazonium bases e.g. $\left[\text{C}_6\text{H}_5-\text{N} \begin{array}{c} \text{---} \\ \text{|||} \\ \text{N} \end{array} \right]^{-} + \text{OH}^{-}$,

which cannot be isolated, however, because these compounds are so very unstable. When caustic soda is added to a solution of a diazonium base, salt formation takes place, which is apparent from the fall in the electrical conductivity of the solution; a *sodium diazotate*, e.g. $\text{C}_6\text{H}_5\text{N}_2\text{ONa}$, is formed. The diazotates are not very stable but in some cases they can be isolated.

Since a strong base like benzenediazonium hydroxide cannot react with caustic soda to form a salt, it must be assumed that this substance is partially converted into *benzenediazohydroxide* $\text{C}_6\text{H}_5-\text{N}=\text{N}-\text{OH}$; the latter compound forms a *diazotate* $\text{C}_6\text{H}_5-\text{N}=\text{N}-\text{ONa}$, with sodium hydroxide, therefore benzenediazohydroxide reacts like a weak acid. When an excess of alkali is added, the sodium diazotate passes over into an isomer, which can be isolated in the solid form. This is called the *iso-diazotate*, while the initial compound is called the normal *diazotate*.

Normal diazotates couple rapidly with phenols in aqueous solution with the formation of *hydroxyazobenzenes*.

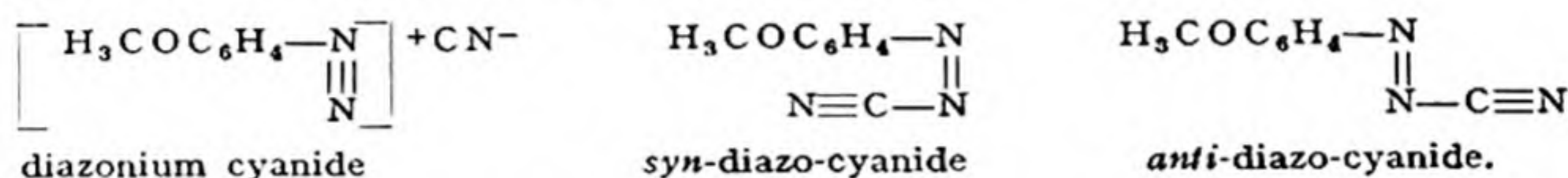
At ordinary temperatures, iso-diazotates either fail to give this reaction or they react only very slowly. The free diazohydroxides are very unstable.

Only in a very small number of cases has it been possible to isolate diazo-hydroxides belonging to the normal diazotates.

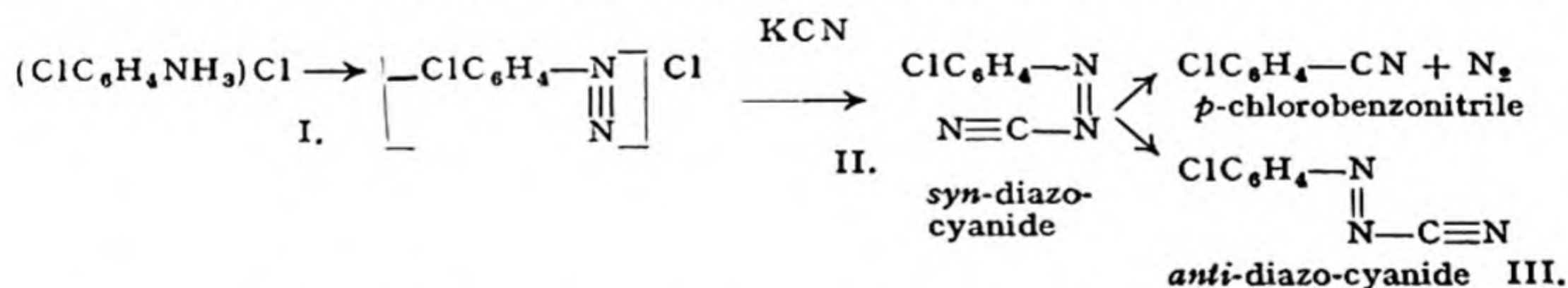
From the above, it follows that diazonium salts are stable in acid solutions (to $p_H=3.5$), normal diazotates in approximately neutral solutions ($p_H=6.5-8$) and iso-diazotates in alkaline solutions ($p_H=8$).

HANTZSCH regarded normal and iso-diazotates as *cis*- and *trans*-isomers, in which the groups C_6H_5 and ONa are situated in *cis*- and *trans*-positions with respect to the plane of the double bond between the two nitrogen atoms of the diazo-group. He ascribed the *cis*-structure to the normal diazotates and called them *syn-diazo-compounds*, and the *trans*-structure to the iso-diazotates, which he named *anti-diazo-compounds*.

In support of this view may be mentioned the existence of three isomeric forms of *p*-methoxybenzenediazonium cyanide. By the action of hydrogen cyanide on *p*-methoxybenzenediazonium hydroxide, HANTZSCH obtained a cyanide of the composition $H_3COC_6H_4N_2(CN)(HCN)H_2O$, a colourless crystalline substance, which dissolved in water and was ionised in aqueous solution. This substance had the properties of a diazonium cyanide. On the addition of alkali a yellow diazocyanide was precipitated and this was found to exist in two isomeric forms:

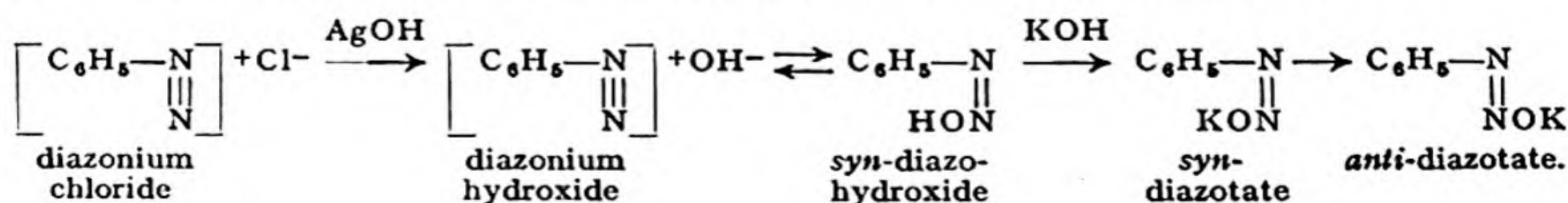


An example of the difference in properties of two isomeric forms of a diazo-compound is to be found in *p*-chlorobenzenediazo-cyanide. When *p*-chloroaniline (I) is diazotised and potassium cyanide is added to the solution, a yellow diazocyanide (II) is produced, which melts at 29° and, at ordinary temperatures, in the presence of copper powder, nitrogen is split off and the substance is converted into *p*-chlorobenzene carbonitrile. This diazo-cyanide must be a *syn*-diazo-compound, for the groups $-CN$ and ClC_6H_4- are situated close to one another and can react with each other very easily:



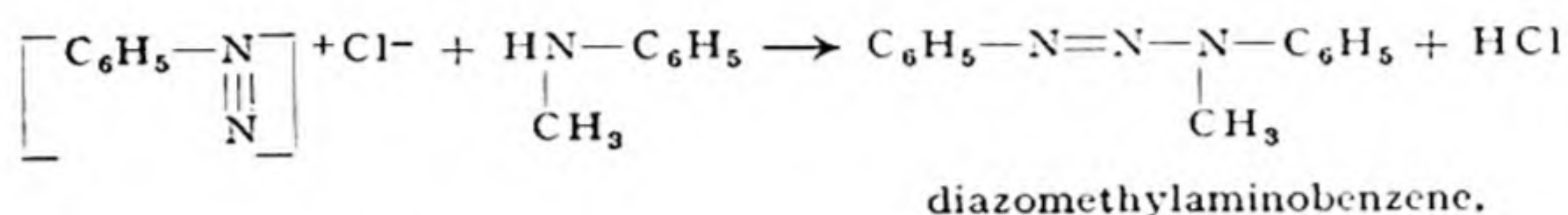
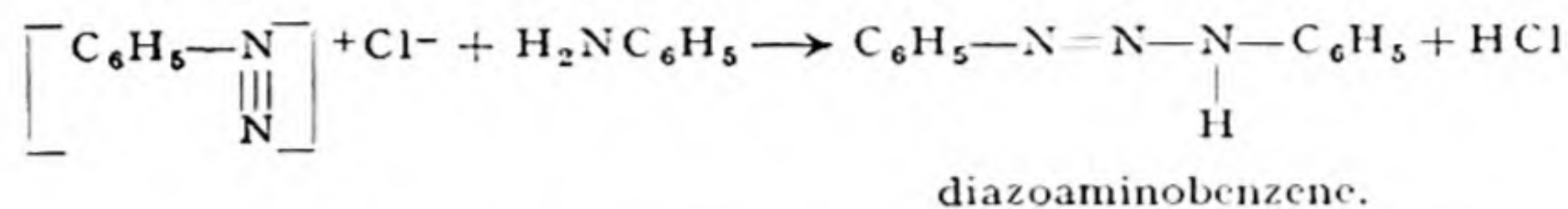
The *syn*-diazo-cyanide is readily converted into an isomer melting at 105° , which is not decomposed by copper powder at ordinary temperatures. In this substance the groups $-C \equiv N$ and ClC_6H_4- are in the *trans*-position. This compound is the *anti*-diazo-cyanide (III).

Thus according to the ideas of HANTZSCH, the transformation of diazonium salts into hydroxy-compounds may be represented by the following scheme:

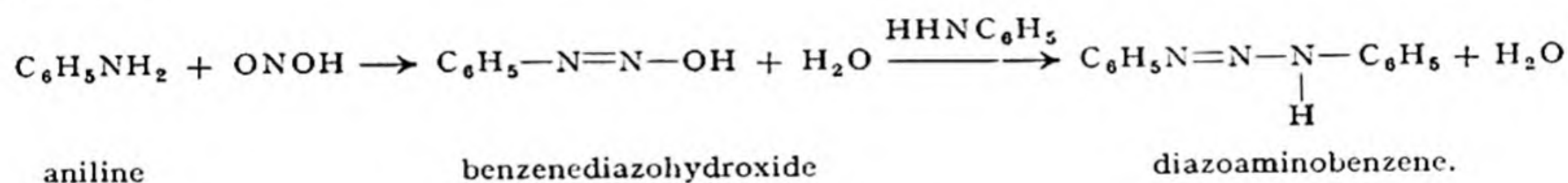


BAMBERGER considers the normal diazotates as compounds derived from diazo-hydroxide $C_6H_4N=N-OH$ and the *iso*-diazotates as derivatives of a nitrosamine C_6H_5NHNO , isomeric with the diazo-hydroxide. The hydrogen atom attached to the nitrogen atom of the nitrosamine would then be replaceable by metals.

Diazoamino-compounds are produced by the action of primary and secondary aromatic amines on diazonium salts in weakly acid solution, in presence of sodium acetate:

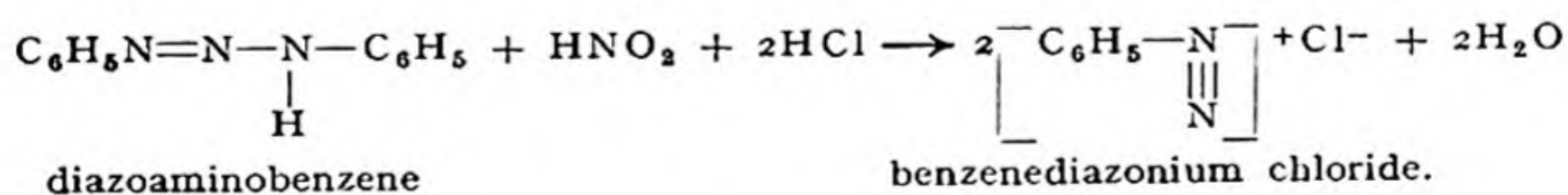


They are also obtained by allowing nitrous acid to react on primary aromatic amines, *e.g.* aniline. It may be presumed that benzenediazo-hydroxide is first produced and immediately reacts with a molecule of aniline:



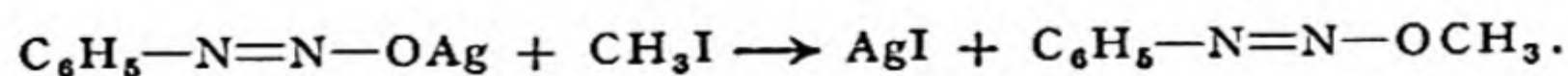
This reaction scheme explains why these compounds are produced on diazotisation in a solution, which is insufficiently acid.

The diazoamino-compounds are yellow, crystalline compounds; they do not combine with acids. The hydrogen atom attached to the nitrogen may be replaced by metals (Cu, Ag and K). They are converted into diazonium salts by the action of nitrous acid in acid solution:



By treatment with an excess of mineral acid or by heating with aniline hydrochloride, diazoamino-compounds are converted into aminoazo-compounds (see 249).

Diazoethers are unstable compounds prepared from silver diazotates and alkyl iodides at low temperature, *e.g.*:



$$\text{C}_6\text{H}_5\text{NH}_2 + \text{ONOH} \rightarrow \text{C}_6\text{H}_5\text{N}(\text{OH})\text{N}=\text{N}-\text{OH} \rightarrow \text{C}_6\text{H}_5\text{N}(\text{O})\text{N}=\text{N}-\text{OH}$$

249. *c. Azo-compounds.* As regards structure these are related to the diazo-compounds. Both nitrogen atoms of the group —N=N— are, however, attached to aromatic nuclei, which may carry substituents. Unlike the diazo-compounds they are quite stable. The simplest compound of this group, azobenzene, has already been discussed in 243. To this same class of azo-compounds belong also the *aminoazo-compounds*, the *hydroxyazo-compounds* and their numerous derivatives including the large group of *azo-dyestuffs* (253).

$$\left[\text{C}_6\text{H}_5-\text{N} \equiv \text{N} \right]^+ \text{Cl}^- + \text{H} \text{---} \text{C}_6\text{H}_4 \text{---} \text{N}(\text{CH}_3)_2 \longrightarrow \text{C}_6\text{H}_5\text{N}=\text{N} \text{---} \text{C}_6\text{H}_4 \text{---} \text{N}(\text{CH}_3)_2 + \text{HCl}$$

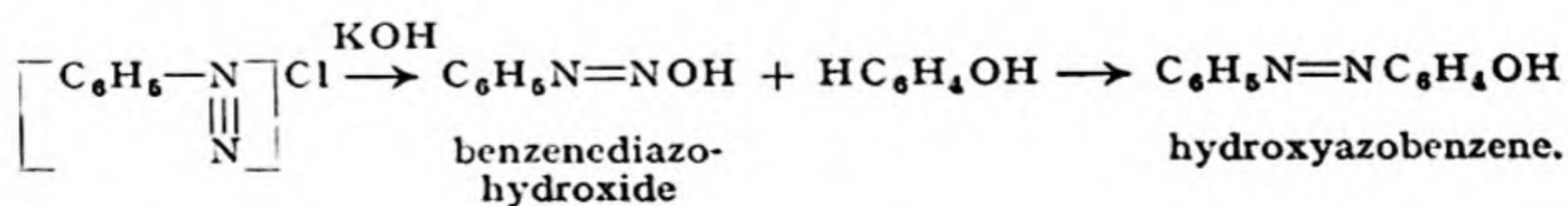
benzenediazonium chloride dimethylaniline dimethylaminoazobenzene.

In this reaction the grouping $\begin{array}{c} -N^+ \\ ||| \\ N \end{array}$ passes over into $-N=N-$.

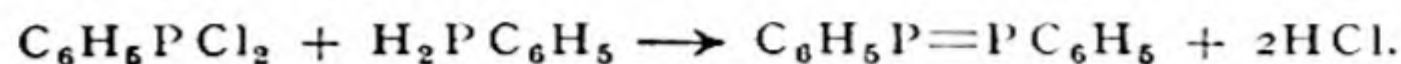
$$\text{C}_6\text{H}_5-\text{N}=\text{N}-\underset{\text{H}}{\text{N}}-\text{C}_6\text{H}_5 \xrightarrow{\text{HCl}} \text{C}_6\text{H}_5\text{NH}_2 + \left[\text{C}_6\text{H}_5-\underset{\text{N}}{\text{N}} \right] \text{Cl} \rightarrow \text{C}_6\text{H}_5\text{N}=\text{NC}_6\text{H}_4\text{NH}_2$$

diazoaminobenzene aminoazobenzene.

Hydroxyazo-compounds are obtained by allowing phenols to react with diazonium salts in weakly alkaline solution. In such a solution benzenediazonium chloride is converted into benzenediazonium hydroxide which reacts with phenol to form hydroxyazobenzene:



Phosphorobenzene $C_6H_5P=PC_6H_5$ is produced by the action of phenylphosphine on *phenylphosphinodichloride* (223, 237):



It is a pale yellow powder, which is soluble in water, alcohol and ether.

Arsenobenzene $C_6H_5As=AsC_6H_5$ is formed by the reduction of phenylarsin oxide C_6H_5AsO with phosphorous acid. It consists of yellow needles, which are converted into phenylarsonic acid $C_6H_5AsO(OH)_2$ by oxidation (223).

THE CONNECTION BETWEEN COLOUR AND STRUCTURE AND THE GENERAL PROPERTIES OF DYESTUFFS

250. For a chemical compound to appear coloured to the eye, it is necessary for it to absorb light of a definite colour from white light: the complementary colour is then observed (see Table 47).

TABLE 47
LIGHT ABSORPTION AND RESULTING COLOURS

Absorption of the substance in the		Observed complementary colour
Violet	4000—4350 Å	Greenish yellow
Blue	4350—4800 „	Yellow
Greenish blue	4800—4900 „	Orange
Bluish green	4900—5000 „	Red
Green	5000—5600 „	Magenta
Greenish yellow	5600—5800 „	Violet
Yellow	5800—5950 „	Blue
Orange	5950—6050 „	Greenish blue
Red	6050—7500 „	Bluish green

Colourless compounds show no selective absorption in the visible region. It has been found that saturated aliphatic hydrocarbons are completely transparent both in the visible and the ultra-violet to 2000 Å, *i.e.* they show no selective absorption (compare 13).

It has already been mentioned (59) that the $>C=O$ group in aldehydes and ketones causes selective absorption in the ultra-violet. Carboxylic acids and esters absorb in the region of 2300–2000 Å, and compounds with the group $-C\equiv N$, $>C=S$ or $-N\begin{smallmatrix} O \\ \diagup \diagdown \\ O \end{smallmatrix}$ also show absorption bands in the ultra-violet; in nitroethane, for example, the maximum absorption lies at 2800 Å.

WITT already observed in 1876 that the colour of coloured organic compounds is connected with the presence in the molecule of certain groups,

402

log E

Fig. 59

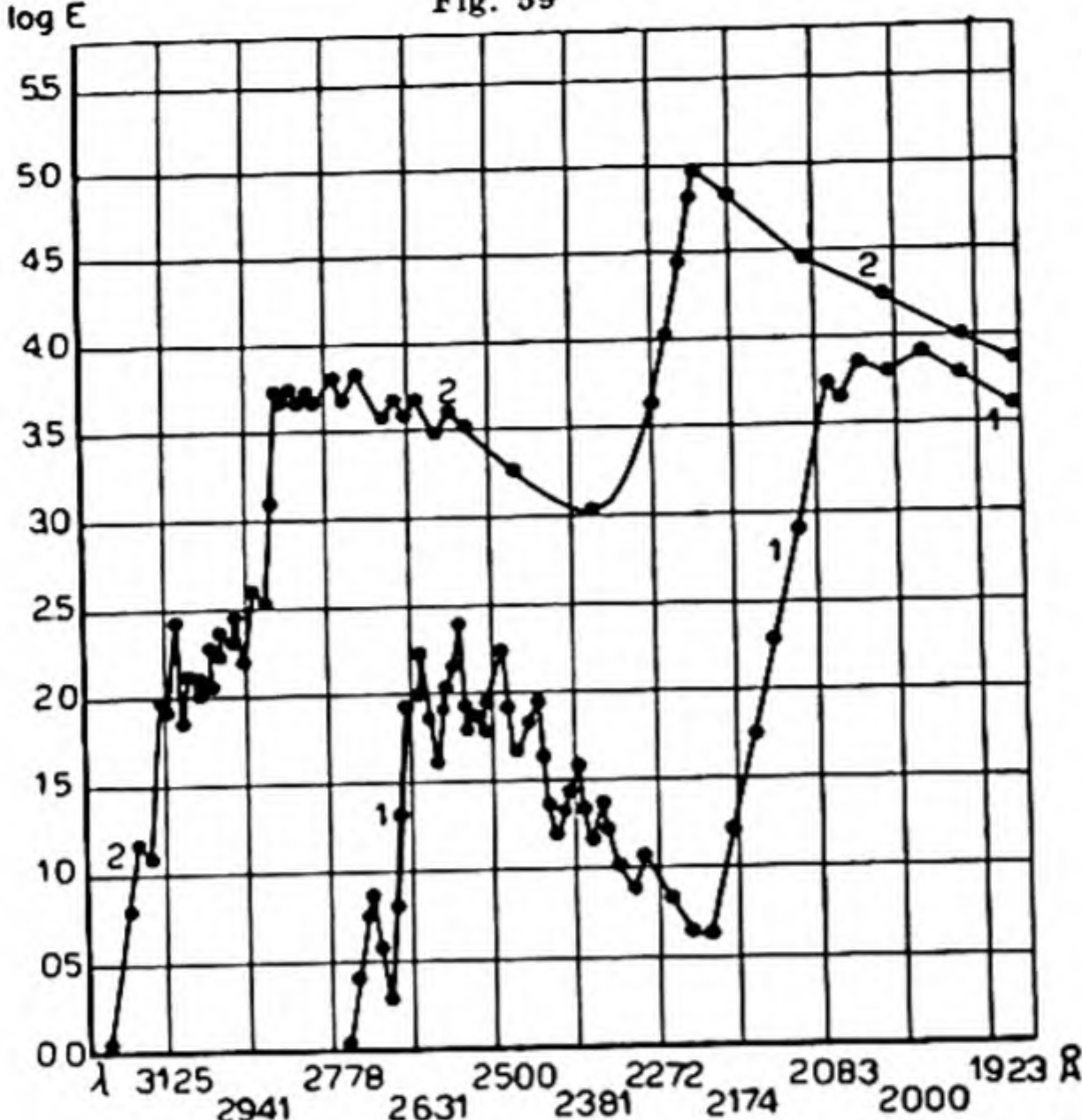
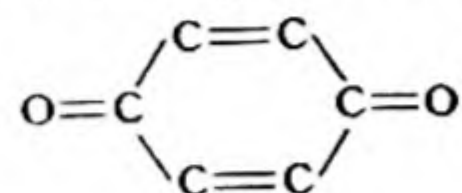


Fig. 59. Absorption curves in the ultra-violet

1 = benzene

2 = naphthalene in hexane

which he called *colour-carrying* or *chromophoric groups*. To these groups belong, *e.g.*, the azo-group —N=N— , the quinonoid group



and the nitroso-group —N=O . The groups mentioned above as causing selective absorption in the ultra-violet, may also be considered as chromophors if the idea of "colour" is extended to

the ultra-violet part of the spectrum. Further, the ring systems of benzene and naphthalene are to be regarded as ultraviolet chromophors; in Fig. 59,

1 represents the extinction $\log E$ curve for benzene and 2 that for naphthalene (solvent hexane). *All these chromophoric groups are unsaturated.*

When a molecule contains one chromophoric group, the absorption band usually lies in the ultra-violet; if two or more chromophoric groups are present, however, in such a position that the double bonds are conjugated, the selective absorption is displaced to longer wave-lengths and an absorp-

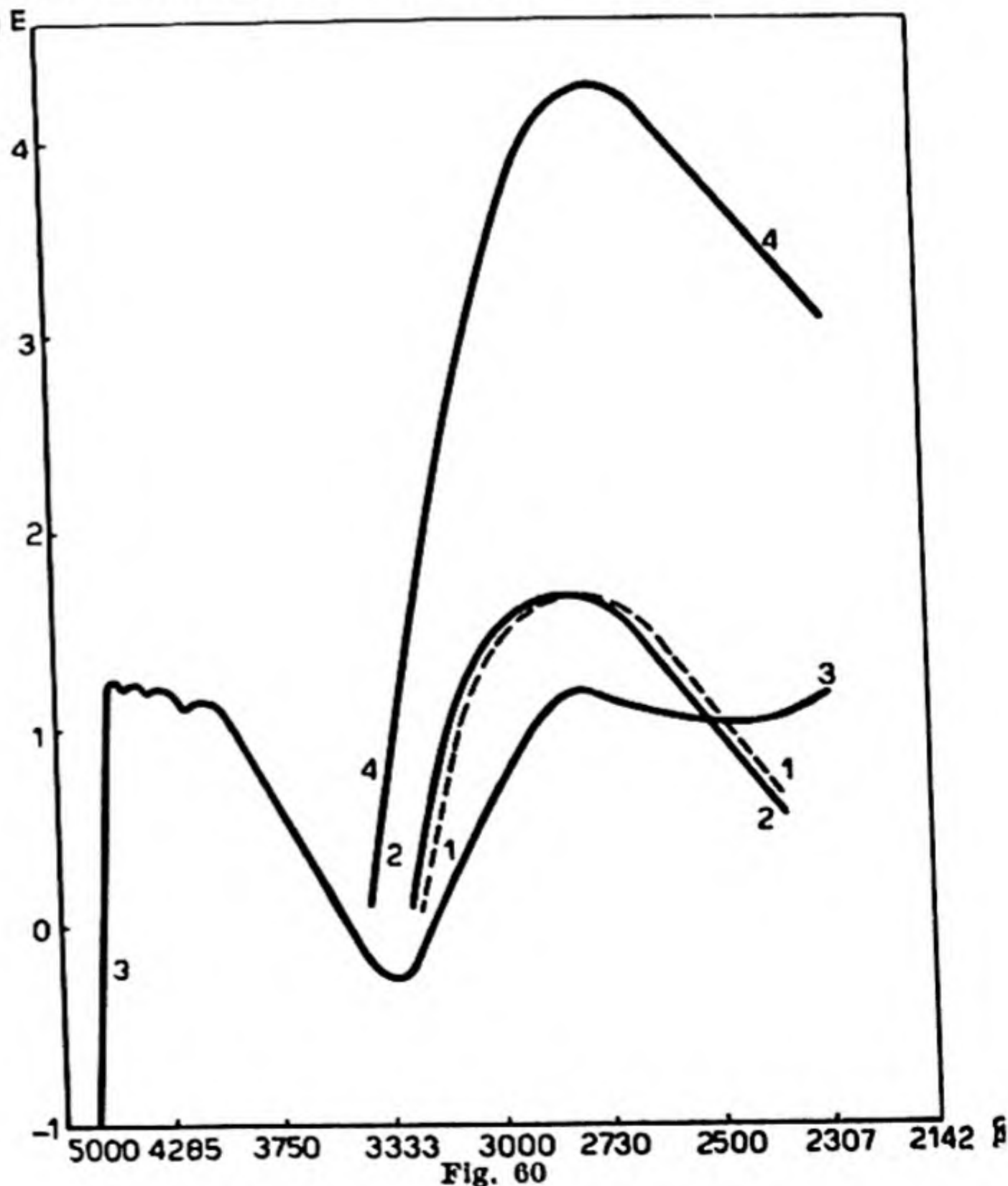


Fig. 60. Absorption curves in the ultra-violet

1 = octan-3,6-dione in hexane

2 = heptanone-4 in hexane

3 = butan-2,3-dione

4 = pentan-2,4-dione

tion band occurs in the visible region. An instructive example of this is to be found in the absorption of ketones and diketones (RAMART-LUCAS).

In Fig. 60, 1 represents the extinction curve for octan-3,6-dione dissolved in hexane, which lies in the ultra-violet and almost coincides with curve 2 for heptanone-4 (compare 59); the concentration of this mono-ketone in hexane is about double that of the octandione. The absorption of the dione, in which the carbonyl groups are separated by two methylene groups, can therefore be expressed as an additive effect of the two separate chromophors (CO-groups). Butan-2,3-dione, on the other hand, in which the grouping $\begin{array}{c} \text{—C—C—} \\ || \quad || \\ \text{O} \quad \text{O} \end{array}$ oc-

curs, shows an absorption band extending to the bluish violet region of the visible spectrum (curve 3); this substance therefore is yellow. The extinction curve 4 for pentan-2,4-dione deviates completely from curves 1 or 2, indicating that pentan-2,4-dione exists mainly in the enol-form (compare table 35 on p. 238).

251. Alkenes show selective absorption in the region of 2200–2000 Å (see curve 2, in Fig. 61 for trimethylethene); for 1,5-hexadiene (curve 1), where the doubly bound carbon atoms are separated by two CH₂-groups, the absorption lies in the same region as for the alkenes. In isoprene (curve 3) and dimethylbutadiene (curve 4), in which conjugated double bonds occur, the absorption bands are displaced towards longer wave-lengths. For these determinations the unsaturated hydrocarbons were dissolved in hexahydrotoluene. When the molecule of an unsaturated hydrocarbon contains a number of conjugated double bonds, as in the fulvenes (289) and the carotenes (308), absorption occurs in the visible region so that such hydrocarbons are coloured.

The colour of quinone is caused by the presence of two >C=O groups conjugated through carbon double bonds. In Fig. 62, curve 1 represents the extinction curve for *p*-benzoquinone and curve 2 that for *o*-benzoquinone (both in hexane).

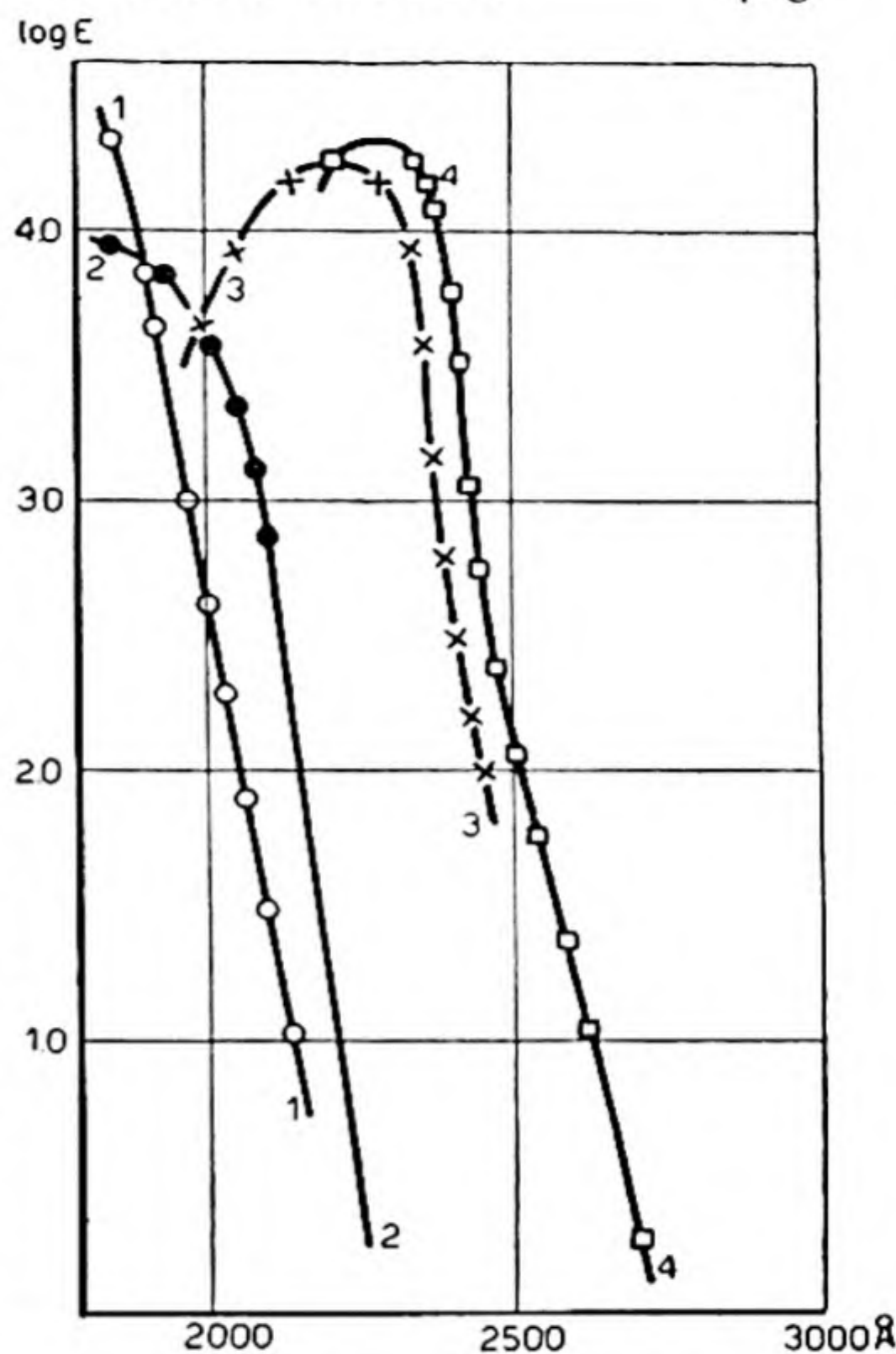


Fig. 61. Absorption curves in the ultra-violet

- 1 = 1,5-hexadiene
- 2 = trimethylethene
- 3 = isoprene
- 4 = 2,3-dimethylbutadiene-1,3

The dyestuffs themselves, comprising large groups of compounds of very varied chemical structure, all contain aromatic ring systems and, in addition,

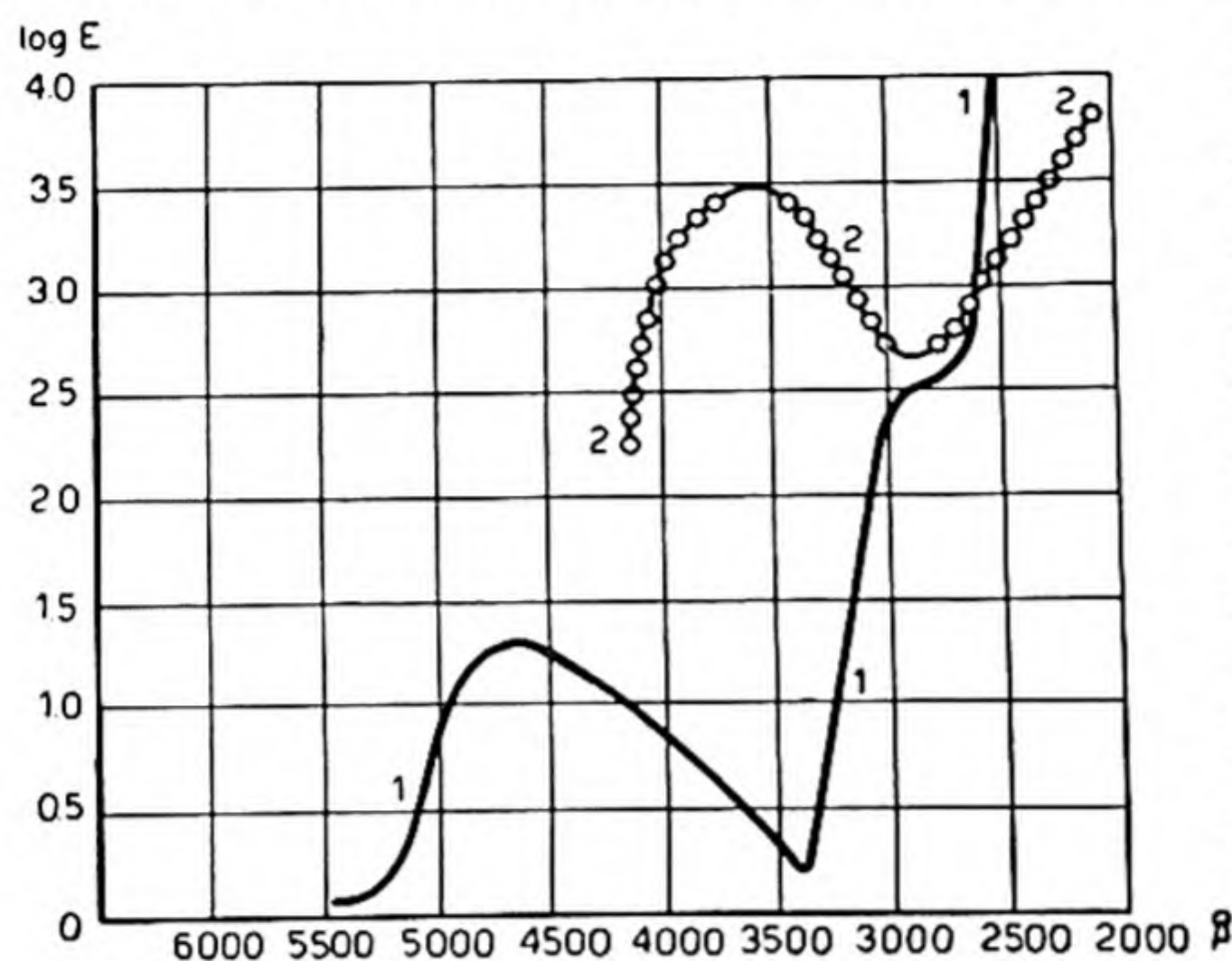


Fig. 62. Absorption curves in the ultra-violet
1 = *p*-benzo-quinone in hexane
2 = *o*-benzo-quinone in hexane

seen that the high absorption maximum of azobenzene lying at 3250 Å (curve 1), is displaced to 3500 Å in the case of *p*-hydroxyazobenzene (curve 2), while *p*-aminoazobenzene shows a deep and broad absorption band with a maximum at 4000 Å.

When the absorption band shown by a compound is displaced in the direction from violet towards green on the introduction of a substituent, the colour changes from greenish yellow towards red, *i.e.* towards lower frequencies; in such a case, on analogy with an expression borrowed from acoustics, the colour is said to be *deepened* or the substituent is said to have a *bathochromic effect*. In the converse case, the substituent causes a *lightening in colour* or a *hypsochromic effect*.

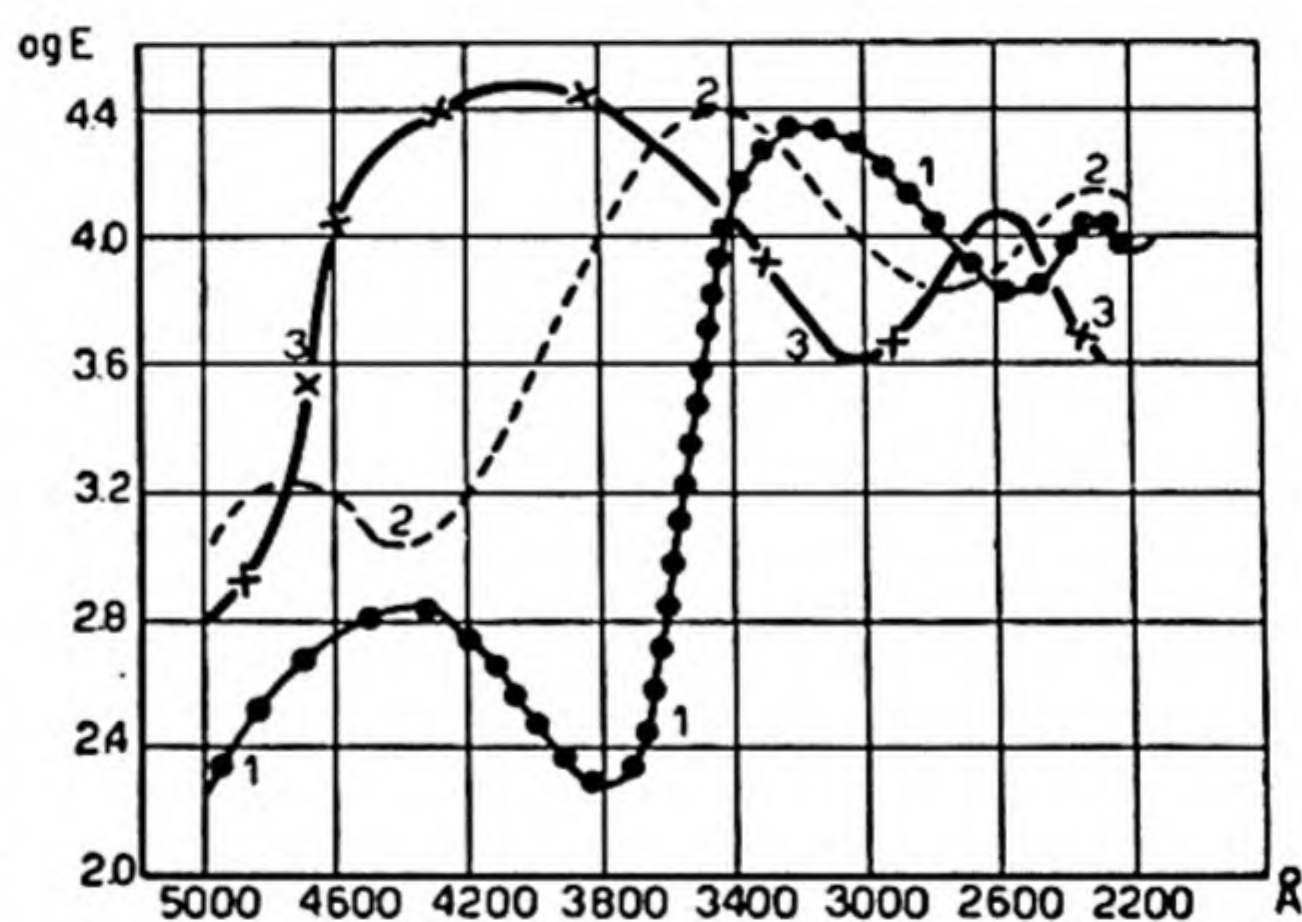


Fig. 63. Absorption curves in the ultra-violet
1 = azobenzene
2 = *p*-hydroxyazobenzene
3 = *p*-aminoazobenzene

In 82 it is mentioned that "loosely bound" π -electrons are associated with doubly bound atoms. These π -electrons can be brought to a higher energy level by absorption of light energy. The necessary light frequency for this to occur, is lower than in the case of light absorption by the σ -elec-

other chromophoric groups, *e.g.* the azo-group or quinonoid groups of various types. In many dyestuffs the presence of an *auxochromic group* (WITT) is necessary besides the chromophoric group; the auxochromic groups have basic or acidic properties and include the amino-group, the phenolic hydroxyl group, the sulpho-group and the carboxyl group. The presence of these groups intensifies the selective absorption and displaces it in the direction of longer wavelengths. In Fig. 63 it may be

trons of the single atom-bond. Since all chromphoric groups contain doubly bound atoms, it explains why these groups cause selective absorption in the near ultra-violet or visible regions. The σ -electrons of the single bond can be brought to a higher energy level only by light of very high frequency; consequently saturated compounds (alkanes) show selective absorption only in the extreme ultra-violet (below 2000 Å).

Auxochromic groups contain atoms possessing one or more lone pairs of electrons (28) (N, O, S); as a consequence, the number of possible mesomeric states is greater, which results in the selective absorption being intensified (cf. also 275).

Dyestuffs and dyeing

252. The use of coloured materials for dyeing domestic articles, especially woven fabrics, can be traced back to prehistoric times. In order to be of use for dyeing textile goods, a compound must not only possess a sufficiently intense colour, but it must also attach itself to the fibre. It must not be removed by washing, *i.e.* it must be wash-fast and it must not be bleached by sunlight, *i.e.* it must be light-fast. The attachment of the dyestuff to the textile fibres is brought about by the auxochromic groups in many kinds of dyestuffs. Thus there are *basic dyes* containing one or more NH_2 -groups or R_2N -groups and *acid dyes* containing one or more acid groups like $-\text{COOH}$, $-\text{SO}_3\text{H}$ or phenolic $-\text{OH}$.

Animal fibres, of which wool and silk are the most important, consist of proteins having an amphoteric character; these fibres can therefore combine with both acid and basic dyestuffs. It has been found that wool and silk take up acid dyes in the ratio of their equivalent weights as acids independent of the chemical nature of the dyestuff. Hence, with respect to acid dyestuffs, the animal fibre behaves like a base (K. H. MEYER).

Vegetable fibres, to which belong cotton, flax, hemp and jute, consist of cellulose, while artificial fibres may consist of regenerated cellulose or one of its derivatives, *e.g.* acetate silk. In all these fibres the dyestuff can be retained only by absorption or by solid solution unless the fibre has been pretreated with a fixing agent.

Cotton fabrics can be dyed directly only by certain kinds of dyestuffs. In this case it is mainly absorption which occurs. The *benzopurpurins* (283) belong to these direct or "substantive" dyes for cotton, which usually possess colloidal properties. In all other cases where the dyestuffs have no substantive properties, the cotton fabric must be pretreated before dyeing with a fixing agent or "mordant"; mordants are usually composed of salts of weak bases. The fabric is steeped in a solution of an easily hydrolysable metal salt, *e.g.* the acetates of Al , Fe^{III} , Cr^{III} or Sn^{IV} , and then treated

with superheated steam. The colloidal, basic metal salts so produced, attach themselves firmly to the fibre. When fabric treated in this way is dyed, an insoluble complex compound of dyestuff and metal oxide is formed. Many azo-dyestuffs are used as mordant dyes, as is also alizarin (283). Two other methods of dyeing, in which the dyestuff is produced on the fibre, depending respectively, on the use of certain azo-dyestuffs, as "developed dyestuffs" (see 253), and on the use of vat dyes (see 316), are of great importance.

Azo-dyestuffs

253. The simplest *azo-dyestuffs* are azobenzenes in which some of the hydrogen atoms are replaced by amino-, sulpho- or hydroxyl-groups. An important group of azo-dyes are naphthalene derivatives obtained by coupling naphthols or naphthylamines (281) with diazonium salts.

When a diazonium salt is allowed to react with an aromatic amine or a phenol, a basic dyestuff is produced in the former case and an acid dyestuff in the latter. In the formation of *hydroxyazo-dyestuffs* coupling occurs mainly at the *para*-position of the phenol. Coupling in the *ortho*-position does not usually occur in benzene derivatives, and when it does, only to a slight extent, but it takes place to a larger extent with naphthalene derivatives. This method of coupling can be varied very widely, since practically all diazonium salts can be made to react with the most varied substituted anilines or naphthylamines and phenols or naphthols.

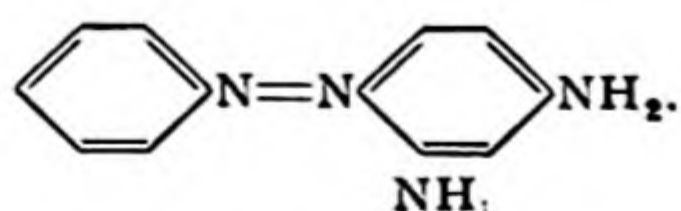
For the preparation of *aminoazo-dyestuffs* an aqueous solution of the diazonium chloride is mixed with a solution of the salt of the aromatic amine to be coupled *e.g.* dimethylaniline or *m*-phenylenediamine, and the dyestuff is precipitated by the addition of salt (salting out).

For the preparation of *hydroxyazo-dyestuffs* a solution of the diazonium chloride cooled in ice, is slowly added drop by drop to an *alkaline* solution of the phenol or naphthol or one of their sulphonic acids. The solution must always remain alkaline otherwise the liberated hydrochloric acid will hinder the formation of dyestuff; when coupling is complete the dyestuff is precipitated by adding salt.

Basic azo-dyes

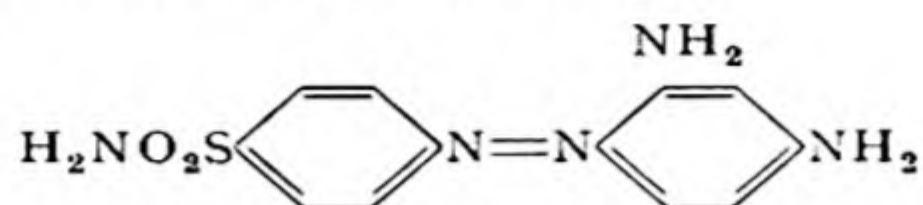
254. *Aniline yellow*, *p*-aminoazobenzene (see 249) the simplest basic azo-dyestuff colours the fibre yellow but has now been superseded by other yellow dyestuffs.

Chrysoidine, *diaminoazobenzene* is produced from benzenediazonium chloride and *m*-phenylenediamine:



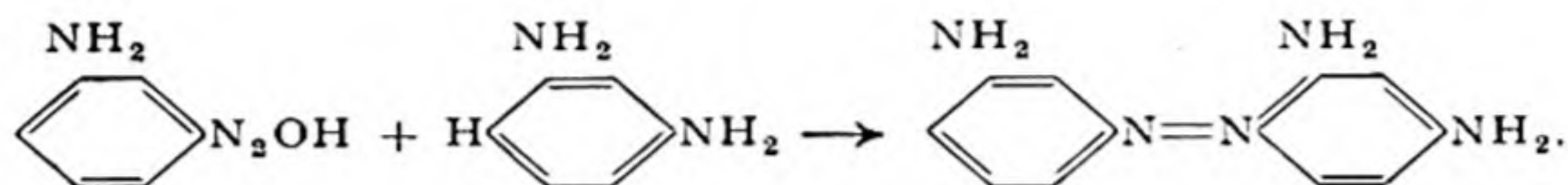
It is fairly readily soluble in water and dyes wool and silk directly. It dyes cotton brownish red after mordanting with tannin.

A sulphonamide derived from chrysoïdine, viz.

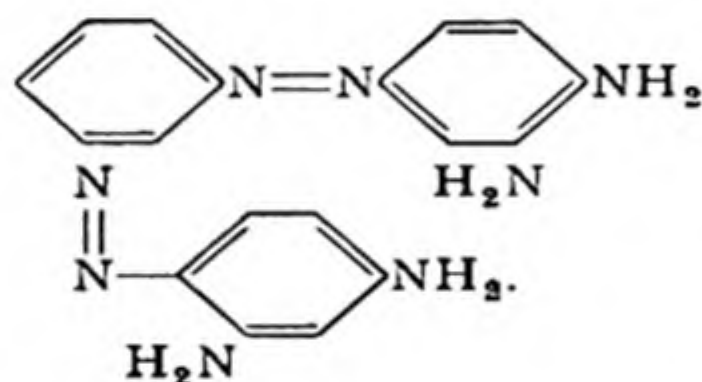


is used in medicine to combat diseases caused by streptococci and coli bacteria. This and related compounds are known under the name of *prontosils* (DOMAGK, 1935; see antibiotics 241, 322 and 335).

Bismarck brown is obtained by treating an aqueous solution of *m*-diaminobenzene with nitrous acid. A mixture of various compounds is produced, amongst which is triaminoazobenzene from diazotised *m*-diaminobenzene and another molecule of the same base:



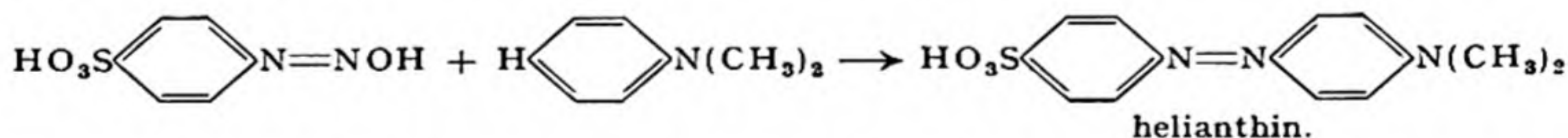
The greater part of Bismarck brown consists of complicated substances, both amino-groups in the *m*-phenylenediamine being diazotised (tetrazotised) and the resultant compound coupling with two molecules of the diamine to give:



It is used for dyeing leather and for the synthesis of poly-azo-dyestuffs:.

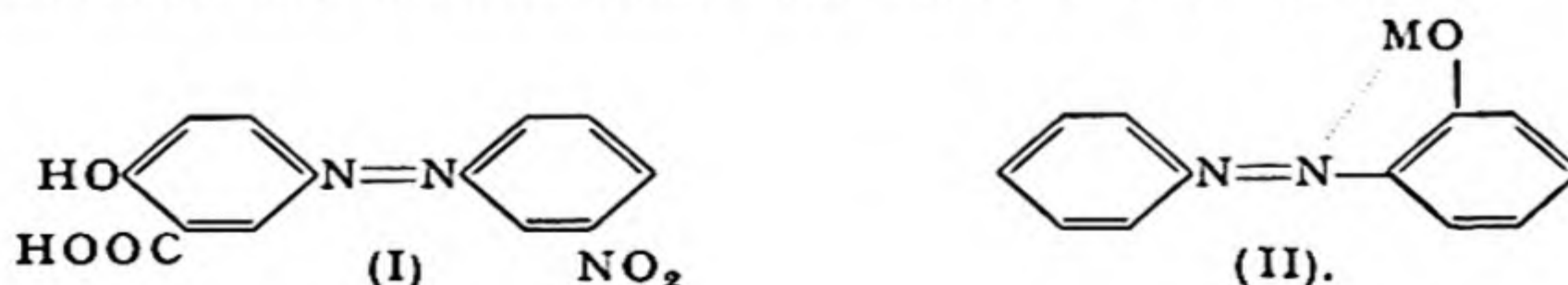
Acid azo-dyestuffs

255. *Helianthin*, dimethylaminoazobenzenesulphonic acid is obtained by adding a solution of diazotised sulphanilic acid (see 241) in hydrochloric acid, to a solution of dimethylaniline in the same medium, and making the mixture alkaline:



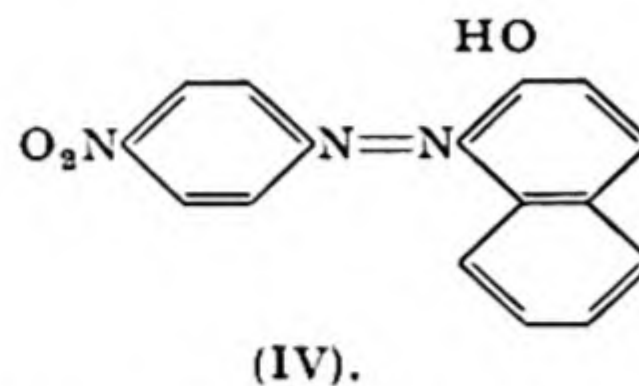
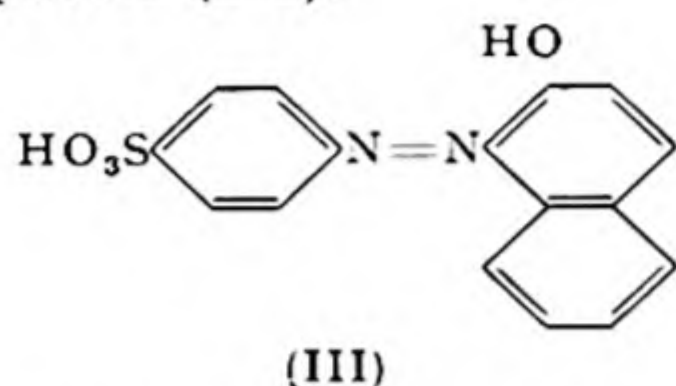
It is not used as a dyestuff, but its sodium salt, *methyl orange*, is used as an indicator. This salt is yellow in solution and the latter turns red with acid. The colour change occurs at $\text{pH} = 4$, i.e. on the acid side and is caused by salt formation on the weakly basic dimethylamino-group; the degree of dissociation of the strongly acid sulphonyl group is not affected by addition of hydrogen-ions.

Alizarin yellow GGW, a yellow dyestuff (I) once much used for printing on cotton, is produced from diazotised *m*-nitraniline and salicylic acid (263):



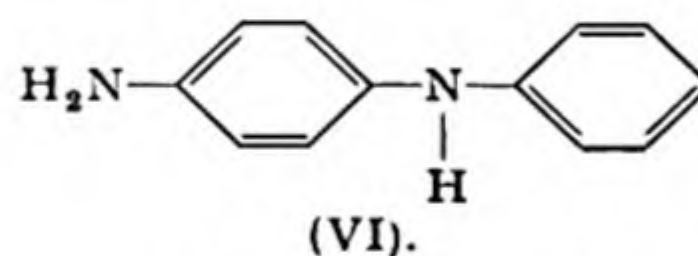
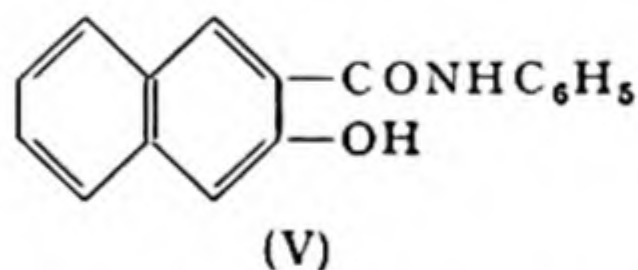
This dyestuff is used as a mordant dyestuff, the HO- and COOH-groups in the *ortho*-position form a complex compound with the metal oxide. Many *o*-hydroxyazo-dyestuffs are used as mordant colours, a complex compound of the type (II) being formed, in which bonding occurs between the metal atom M and the nitrogen atom (compare complex salts of amino-acids 194).

Orange II or β -naphthol orange (III) is produced from diazotised sulphanilic acid and β -naphthol (281):

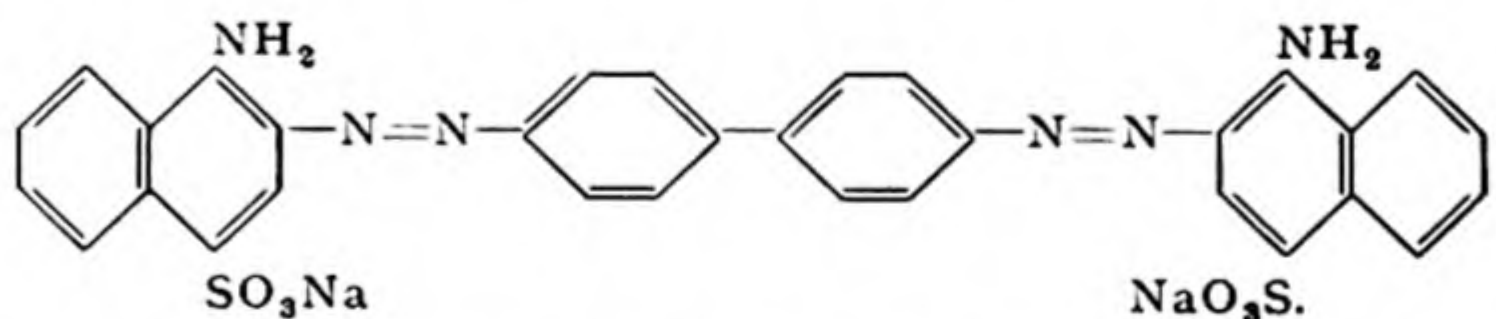


Nitraniline red (Para Red, (IV) is an example of a developed dyestuff. It is insoluble and is therefore formed directly on the fibre by first impregnating the latter with an alkaline solution of β -naphthol, and subsequently treating the dried fabric with a solution of diazotised *p*-nitraniline. This type of dyestuff is also known as an *ice colour*, from the use of ice in the bath of diazotised amine.

Important developed colours (ice colours) are obtained by steeping the fabric in an alkaline solution of the anilide of 2,3-hydroxynaphthoic acid (V)—which is known technically as *Naphthol AS*—and then coupling the prepared cloth with a diazocomponent; thus with diazotised *p*-aminodiphenylamine (VI), a blue mono-azo-dyestuff is produced.



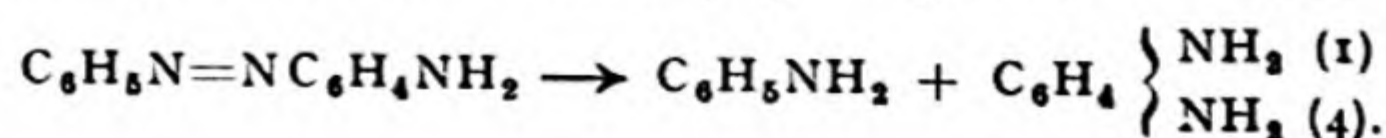
Congo red, which dyes cotton without a mordant like the *benzopurpurins*, is the sodium salt of the acid produced from tetrazotised benzidine (243) and naphthionic acid (281):



The free acid is blue in colour so that the red colour of congo red is changed to blue by mineral acids (use as indicator).

The benzopurpurins are derivatives of congo red, in which each of the benzene nuclei in the benzidine group carries methyl groups; they are less sensitive to acids than congo red.

Azo-dyestuffs, as derivatives of azobenzene, are split up into amino-compounds by powerful reducing agents like tin and hydrochloric acid. Aminoazobenzene gives aniline and *p*-phenylenediamine:



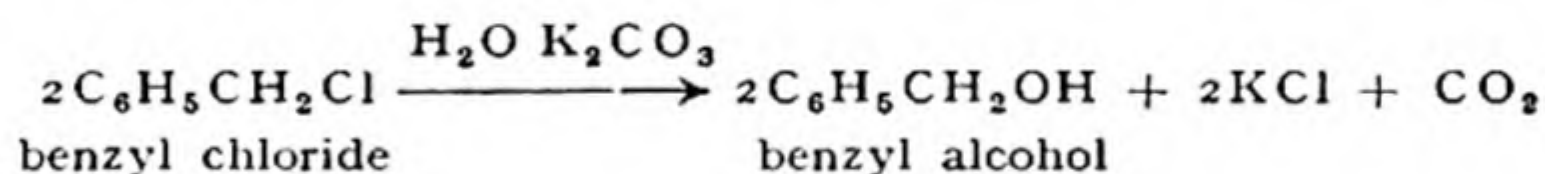
Reductive fission of these dyestuffs is a means of determining their structure and the way in which they have been obtained. For example, if on reduction there is obtained a mixture of equivalent quantities of di- and tri-aminobenzene, then the structure is $\text{H}_2\text{NC}_6\text{H}_4\text{N}=\text{NC}_6\text{H}_3(\text{NH}_2)_2$, since the molecule splits at the azo-double bond. From this it may be concluded that the dyestuff must be obtained from diazotised diamino-benzene coupled with a second molecule of diaminobenzene.

(x) AROMATIC ALCOHOLS

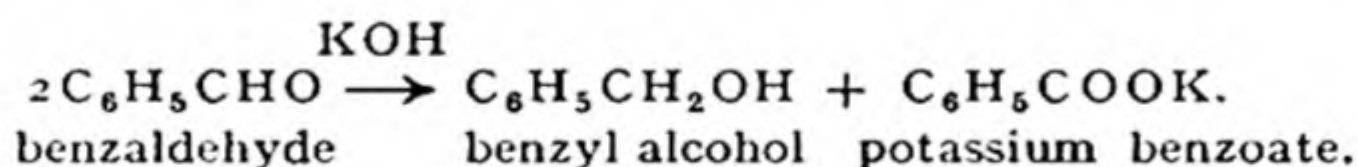
256. These compounds are derivatives of toluene or its homologues containing a hydroxyl group in the alkyl side-chain. Hence they contain the group $-\text{CH}_2\text{OH}$ and show the characteristic properties of primary alcohols. These aromatic alcohols can be oxidised to the corresponding aldehydes and carboxylic acids; they can form ethers and esters. On the other hand, they are *not* like phenols; they are not soluble in alkalis and they do not give the colouration with ferric chloride characteristic of phenols.

Phenylmethanol or *benzyl alcohol* $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$, the simplest compound of this series, occurs in Peru- and tolu-balsams and, both as the free alcohol and as the acetate, benzoate and cinnamate esters in oil of jasmine and other essential oils.

Benzyl alcohol is obtained by heating phenylchloromethane (benzyl chloride) with aqueous potassium carbonate:

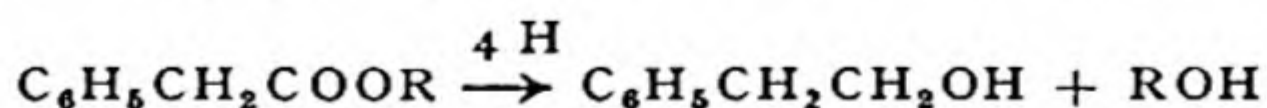


or by treating benzaldehyde (**257**) with concentrated potash (CANNIZZARO reaction):

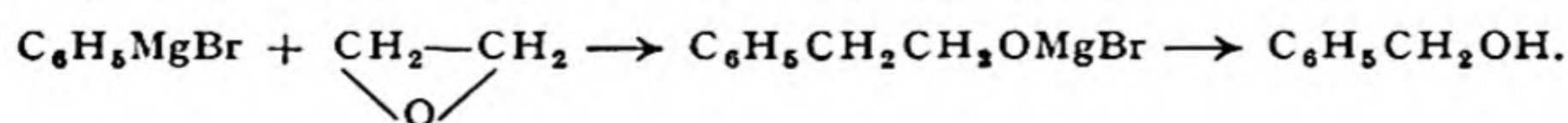


Benzyl alcohol is a liquid boiling at 206° and is sparingly soluble in water; it, and some of its esters, are used in the perfumery industry. It is converted into resinous products by concentrated sulphuric acid.

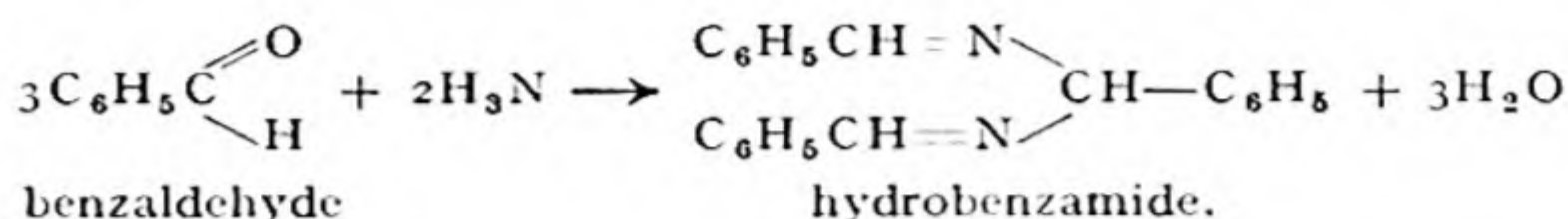
Phenylethyl alcohol $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{OH}$ occurs in oil of roses and is prepared commercially by reduction of ethyl phenylacetate with sodium and alcohol:



or from phenylmagnesium bromide and ethylene oxide:



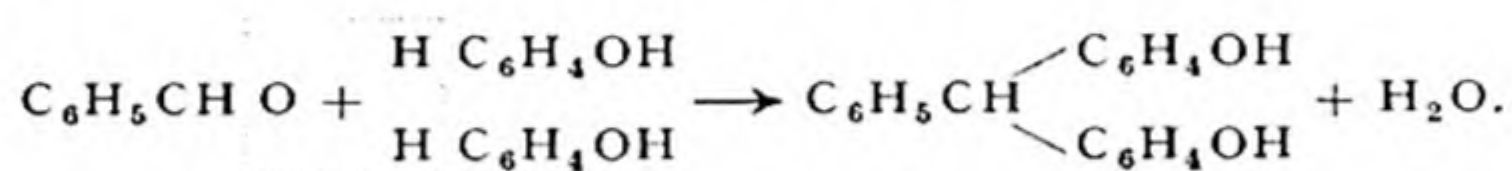
hydrobenzamide $(C_6H_5CH)_3N_2$, is formed from three molecules of benzaldehyde and two of ammonia:



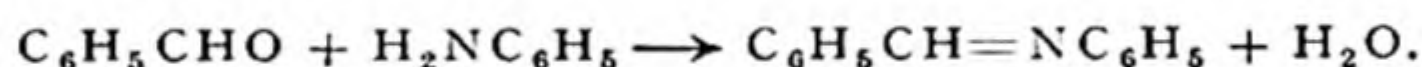
A characteristic reaction for aromatic aldehyde occurs in their behaviour towards alcoholic potash when they undergo the CANNIZZARO reaction (61).

The striking fact that benzaldehyde does not reduce FEHLING'S solution is probably caused by the benzaldehyde being rapidly converted into benzyl alcohol and potassium benzoate by the alkaline solution.

Aromatic aldehydes easily condense with dimethylaniline or phenols to give derivatives of *triphenylmethane* (273):



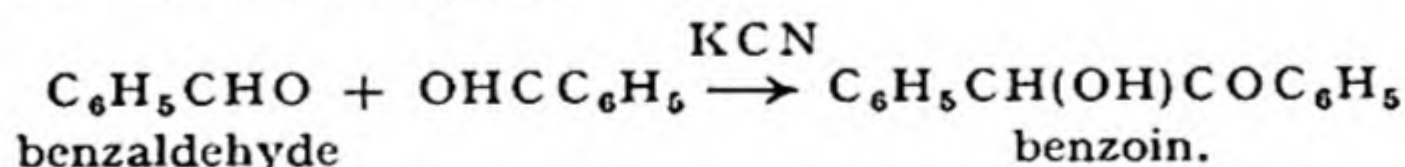
Benzaldehyde reacts very easily with aniline. When equal volumes of the two substances are mixed and gently warmed together, water separates in tiny droplets and *benzylideneaniline*, which crystallises when the mixture is cooled, is formed:



Benzoyl chloride (260) is produced by treating benzaldehyde with chlorine at the boil.

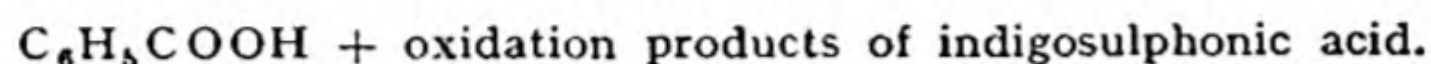
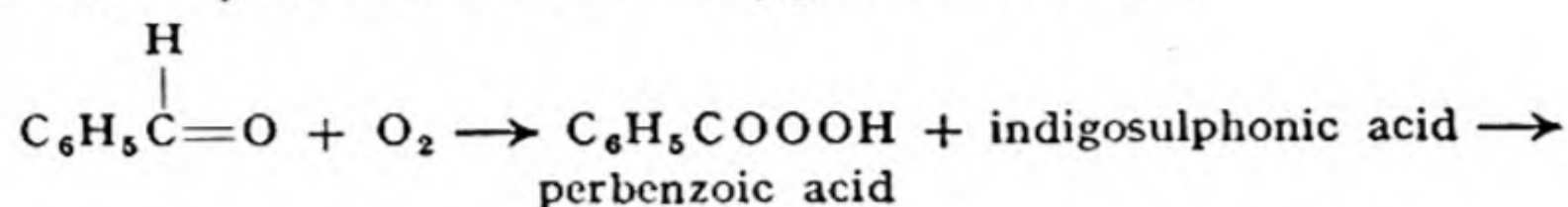
Benzaldehydephenylhydrazone is produced by warming benzaldehyde with a solution of phenylhydrazine in sulphurous acid. It is a pale yellow, crystalline compound melting at 152° , which is converted into a scarlet modification by violet and ultra-violet light and reverts again to the yellow modification in yellow or green light (phototropy).

Aromatic aldehydes undergo self-condensation on warming with potassium cyanide solution, which acts catalytically, to form *ketonic alcohols*; *benzoin* is produced from benzaldehyde:

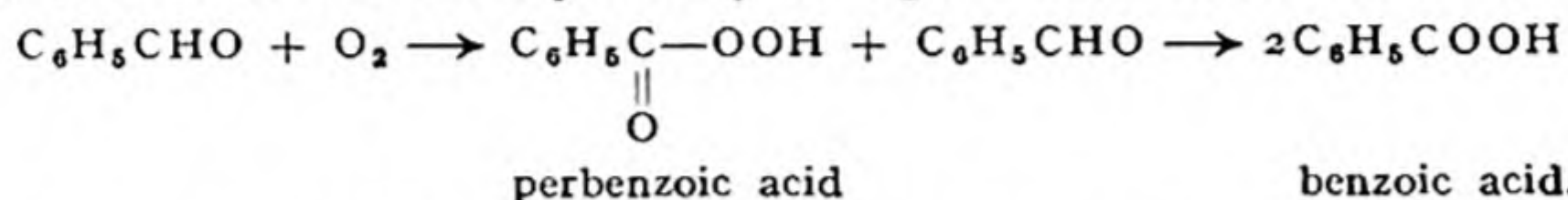


Benzaldehyde is oxidised by atmospheric oxygen. In this reaction, the classical example of *autoxidation*, benzaldehyde takes up a molecule of oxygen and is thereby converted into *perbenzoic acid*, which then decomposes into benzoic acid and oxygen in an activated form. This oxygen may then oxidise another molecule of benzaldehyde to benzoic acid, or it may oxidise another oxidisable substance, if present. JORISSEN introduced benzaldehyde and *indigosulphonic acid* (a blue coloured compound) into

a closed vessel containing air. It was found that the oxygen content gradually decreased and that the oxygen was taken up for the oxidation of benzaldehyde and also for the oxidation of the indigosulphonic acid, which was thereby converted into a colourless product. Under these same conditions indigosulphonic acid was not oxidised. Hence the benzaldehyde acts as an "oxygen activator":



The autoxidation of benzaldehyde may be represented then as follows:

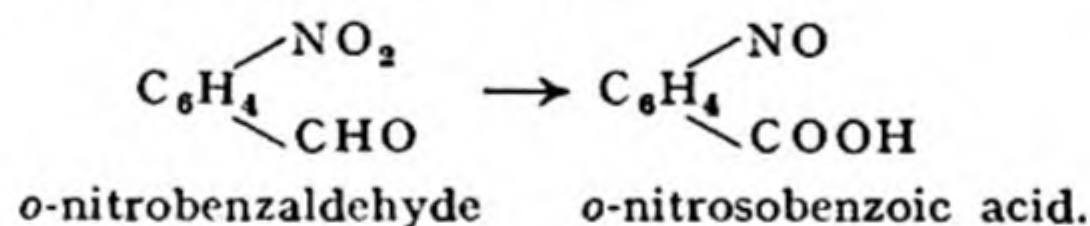


When perbenzoic acid (m.p. 42–43°) is added to an equivalent amount of benzaldehyde, it first of all dissolves and then the mixture soon becomes a solid mass of pure benzoic acid (A. v. BAEYER). The oxidation of benzaldehyde is probably influenced catalytically by traces of iron.

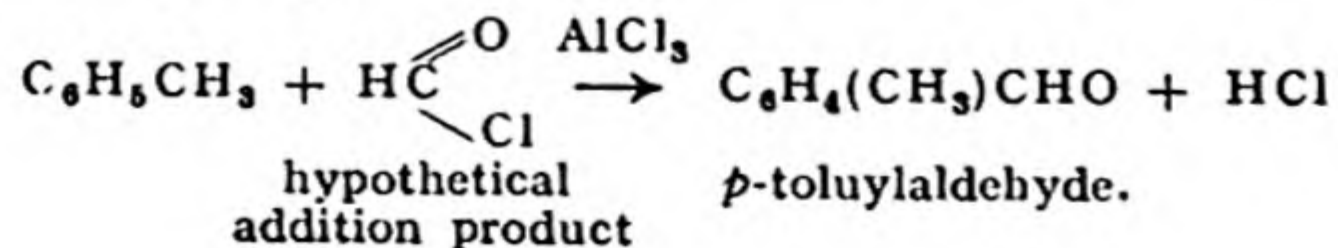
The oxidation of benzaldehyde to benzoic acid is greatly retarded by the addition of quinol (*e.g.* 1/1000th parts. by weight). Catechol and pyrogallol have the same effect and not only on benzaldehyde but on other oxidisable substances like linseed oil and turpentine. MOUREU and DUFRAISSE, who discovered this phenomenon, called the substances, which exert this retarding action, *antioxidants*; in some cases, sodium iodide can act as an antioxidant as well as phenols.

Substituted aldehydes

258. *m*-Nitrobenzaldehyde $\text{C}_6\text{H}_4(\text{CHO})\text{NO}_2$ -1,3, is the chief product formed in the nitration of benzaldehyde, about 20 % of *o*-nitrobenzaldehyde being produced as a by-product. The latter can be made more conveniently by oxidising *o*-nitrotoluene with manganese dioxide and sulphuric acid. On irradiation, *o*-nitrobenzaldehyde is rapidly converted into *o*-nitrosobenzoic acid:

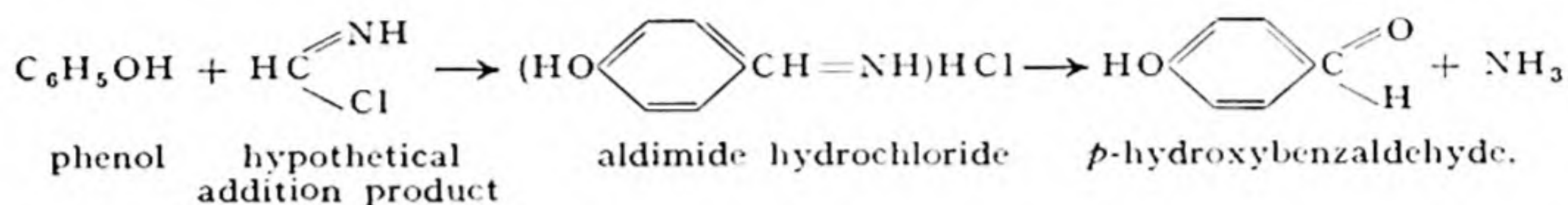


Toluyaldehydes. Homologues of benzaldehyde can be prepared by the action of carbon monoxide and dry hydrogen chloride in the presence of aluminium chloride or copper chloride on aromatic hydrocarbons (GATTERMANN). In this reaction it may be supposed that CO and HCl react like the unknown chloride of formic acid $\text{HC}(\text{O})\text{Cl}$ (cf. the FRIEDEL-CRAFTS synthesis). In this reaction the aldehyde group enters the *para*-position with regard to the alkyl group:



Benzaldehyde can also be prepared by this method if carbon monoxide (and hydrogen chloride) under high pressure is allowed to react at about 70° on benzene in which aluminium chloride is suspended.

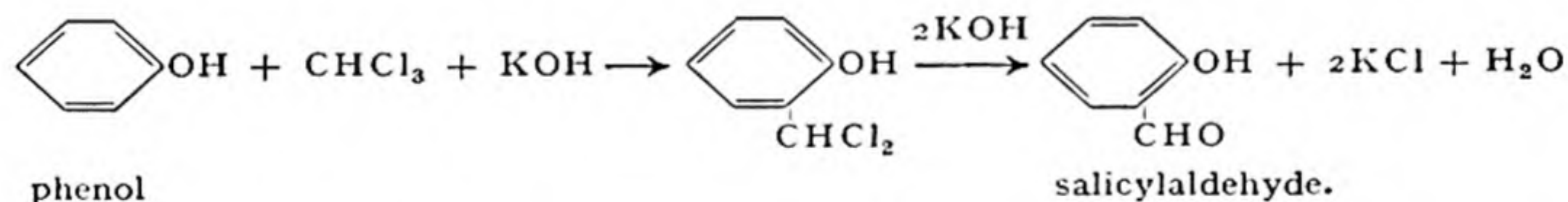
Hydroxy-aldehydes are produced in the same way as the homologues of benzaldehyde, from phenol, liquid hydrogen cyanide, hydrogen chloride and aluminium chloride (GATTERMANN). Hydrogen cyanide and hydrogen chloride together react like the unknown imino-chloride of formic acid $\text{HC} \begin{smallmatrix} \text{=NH} \\ \text{\textbackslash Cl} \end{smallmatrix}$. With phenol this forms an *aldimide* in the form of its hydrochloride, which is hydrolysed by boiling water to aldehyde and ammonia:



This method can also be applied to phenyl ethers when benzaldehydes substituted with alkoxy-groups are produced.

Hydroxy-aldehydes can also be obtained by the method of REIMER and TIEMANN by heating phenols with chloroform and alkali. In this case, *o*-hydroxybenzaldehyde is produced along with a small amount of the *para*-isomer, from phenol.

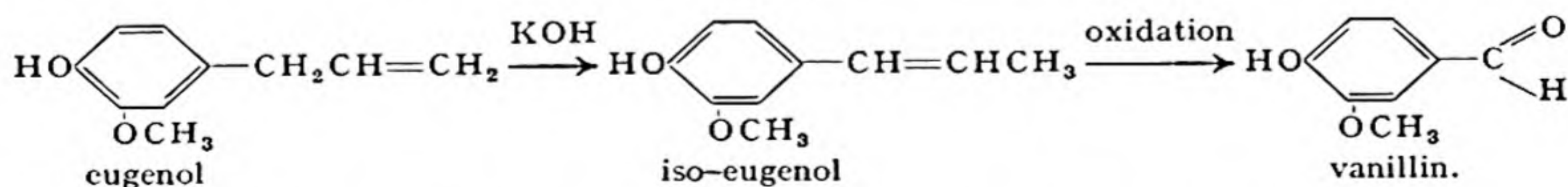
Salicylaldehyde, which occurs in the volatile oil obtained from species of spirea, can be made synthetically by this method:



Salicylaldehyde is a pleasant smelling liquid boiling at 196° and melting at 1.6° . It gives a violet colouration with ferric chloride solution. It is used, for example, for the synthesis of coumarins (269, 327).

Anisaldehyde $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$, a liquid boiling at 248° , is much used as a perfume and occurs in some essential oils.

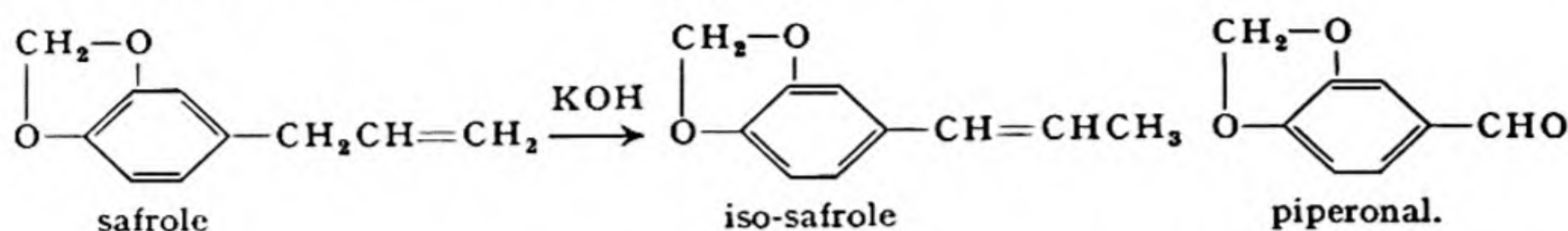
Vanillin, the *mono-methyl ether of protocatechuic aldehyde*, $\text{CH}_3\text{OC}_6\text{H}_3(\text{OH})\text{CHO}$, the odiferous principle of vanilla, is prepared from *eugenol* as follows:



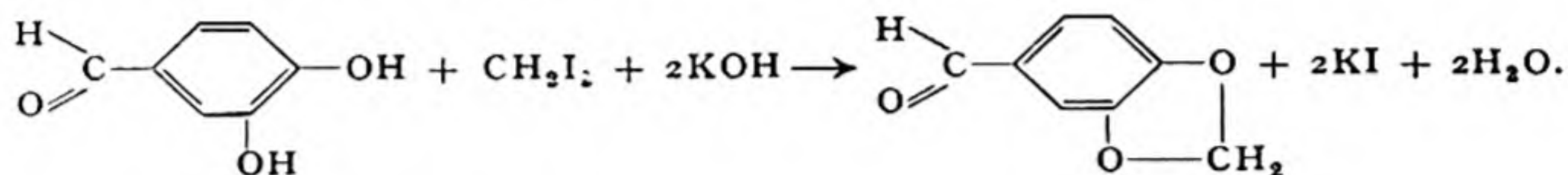
Vanillin melts at 81° and gives a blue colouration with ferric chloride.

Piperonal or *heliotropin* is an important perfume having the scent of heliotrope

flowers. It is prepared from *safrole* (226), which is converted by alkali into *isosafrole* from which piperonal is obtained by oxidation:

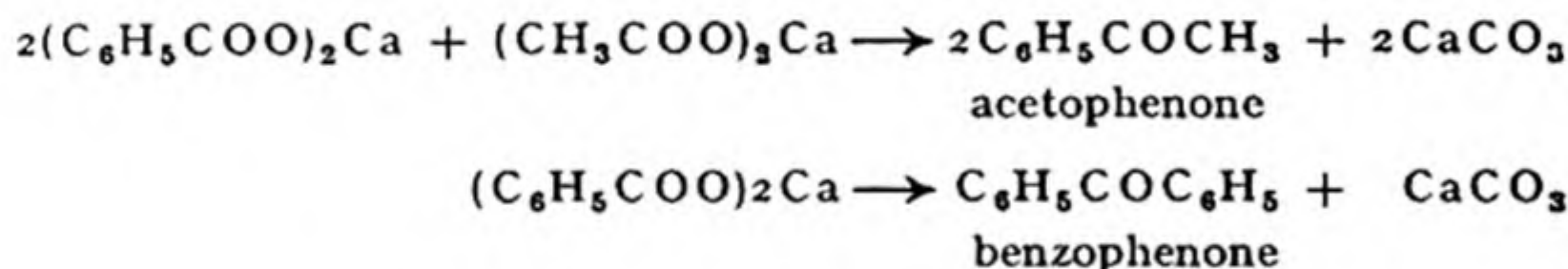


Piperonal melts at 37° and boils at 263° . Its structure follows from its formation from protocatechuic aldehyde by the action of diiodomethane and alkali:

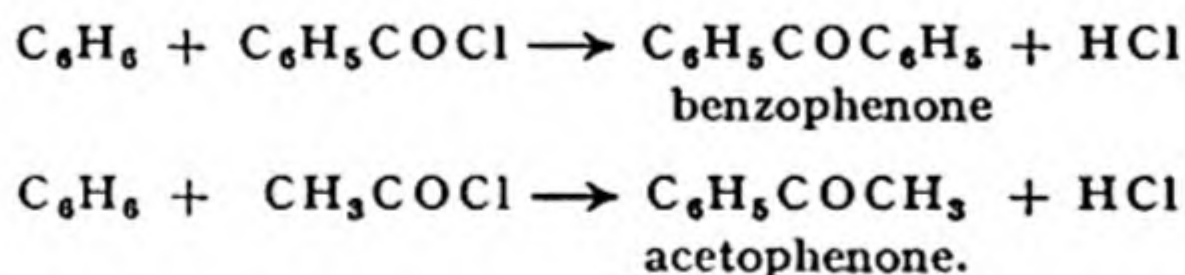


(xii) AROMATIC KETONES AND THEIR DERIVATIVES

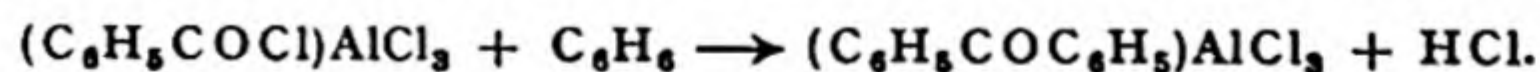
259. Aromatic ketones can be divided into mixed aromatic aliphatic ketones and purely aromatic ketones. The best known of the former kind is *acetophenone*, $\text{C}_6\text{H}_5\text{COCH}_3$ and of the latter, *benzophenone*, $\text{C}_6\text{H}_5\text{COC}_6\text{H}_5$, which are produced, respectively, by heating a mixture of calcium acetate and calcium benzoate and by heating calcium benzoate:



or by the action of aliphatic or aromatic acid chlorides respectively on aromatic hydrocarbons in the presence of an equivalent quantity of anhydrous aluminium chloride (FRIEDEL and CRAFTS; 218):



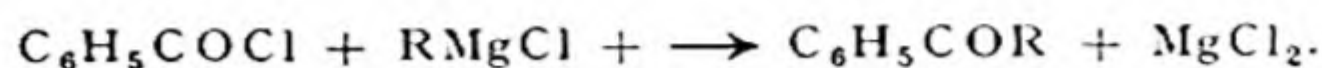
When aluminium chloride is added to one of these acid chlorides, crystalline addition compounds, *e.g.* $(\text{CH}_3\text{COCl})\text{AlCl}_3$ and $(\text{C}_6\text{H}_5\text{COCl})\text{AlCl}_3$, are produced. These addition compounds react with benzene with the elimination of hydrogen chloride and the formation of an addition compound of the ketone with aluminium chloride:



These new addition compounds are decomposed by water giving quantitative yields of ketones, *e.g.* benzophenone (BÖESEKEN, PERRIN; compare 218).

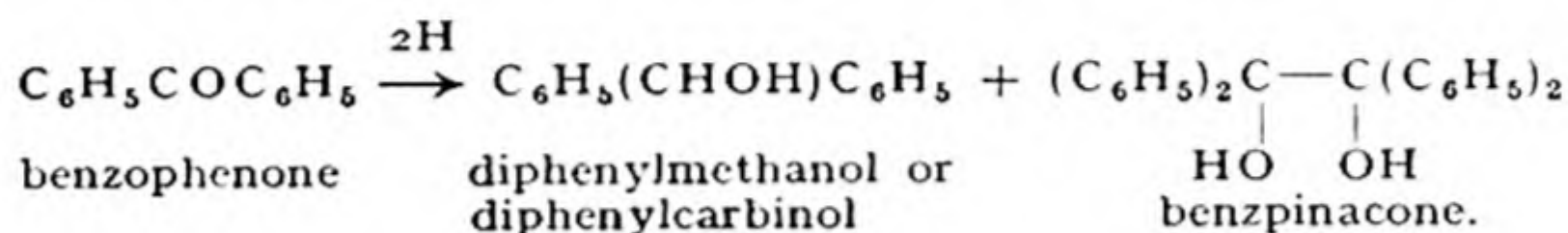
Acetophenone can also be prepared by warming benzene with acetic anhydride and aluminium chloride.

Another method for the preparation of mixed aromatic ketones consists of allowing an acyl chloride, *e.g.* benzoyl chloride (260), to react with an alkylmagnesium halide:



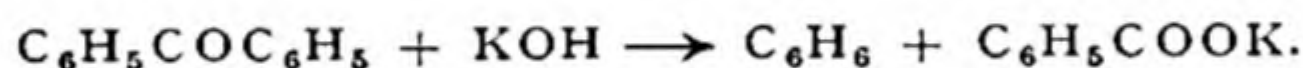
Acetophenone melts at 20° , boils at 200° , is very sparingly soluble in water and has a smell of hay.

The carbonyl group in aromatic ketones has the same properties as in aliphatic ketones; on reduction, aromatic ketones are converted into the corresponding alcohols. In the reduction of benzophenone, *1,1,2,2-tetraphenylethane-1,2-diol* or *benzpinacone* is also formed:

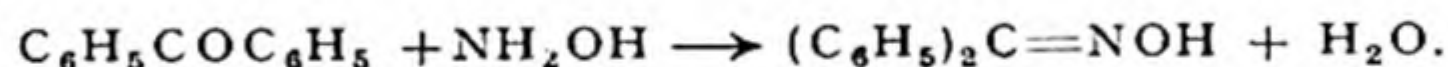


Benzophenone occurs in two modifications, the metastable form melting at 27° and the stable form melting at 40° .

On fusion with potash it gives benzene and potassium benzoate:



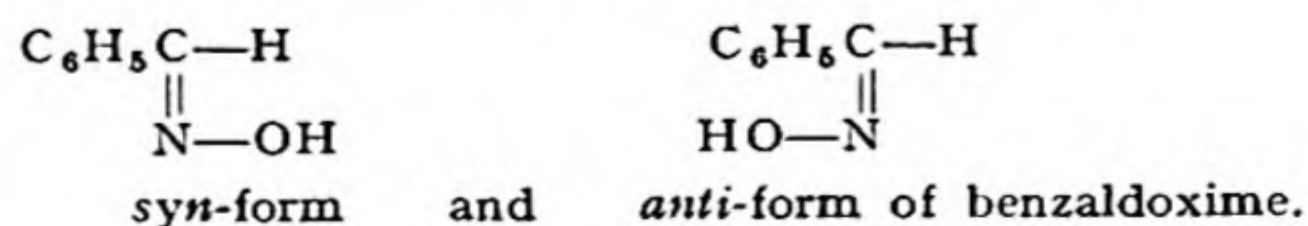
Aromatic oximes are produced by allowing hydroxylamine to react with aromatic aldehydes or ketones:



Some aromatic oximes occur in stereoisomeric forms, *e.g.* benzaldoxime.

No isomeric forms of benzophenoneoxime are known; if, however, one of the phenyl groups carries a substituent, two ketoximes are obtained (compare 140). This is found for example, with the oximes from mono-chloro- and mono-bromo-benzophenone, from tolyl phenyl ketone, $\text{CH}_3\text{C}_6\text{H}_4\text{COC}_6\text{H}_5$, and from anisyl phenyl ketone, $\text{CH}_3\text{OC}_6\text{H}_4\text{COC}_6\text{H}_5$.

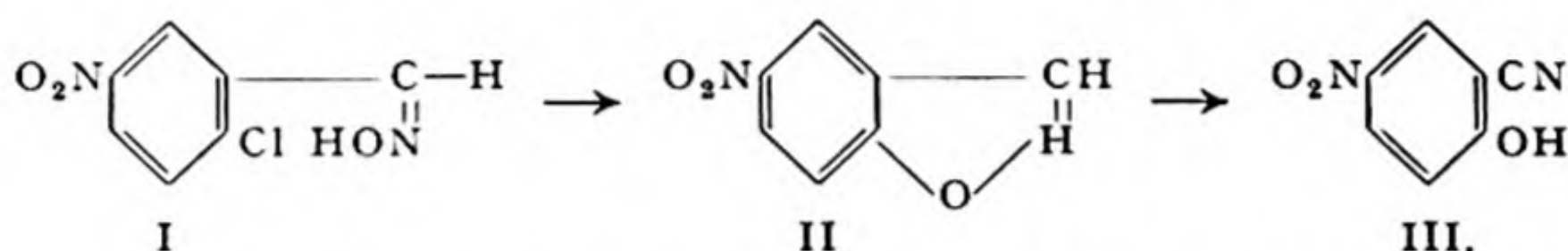
According to stereochemical theory *cis*- and *trans*-isomers are also possible in aldoximes; in many cases, two isomeric forms have been found, which are termed *syn*- or *anti*-aldoximes in accordance with a suggestion of HANTZSCH depending on whether the H and OH lie on the same or on different sides of the plane of the $>\text{C}=\text{H}$ — double bond:



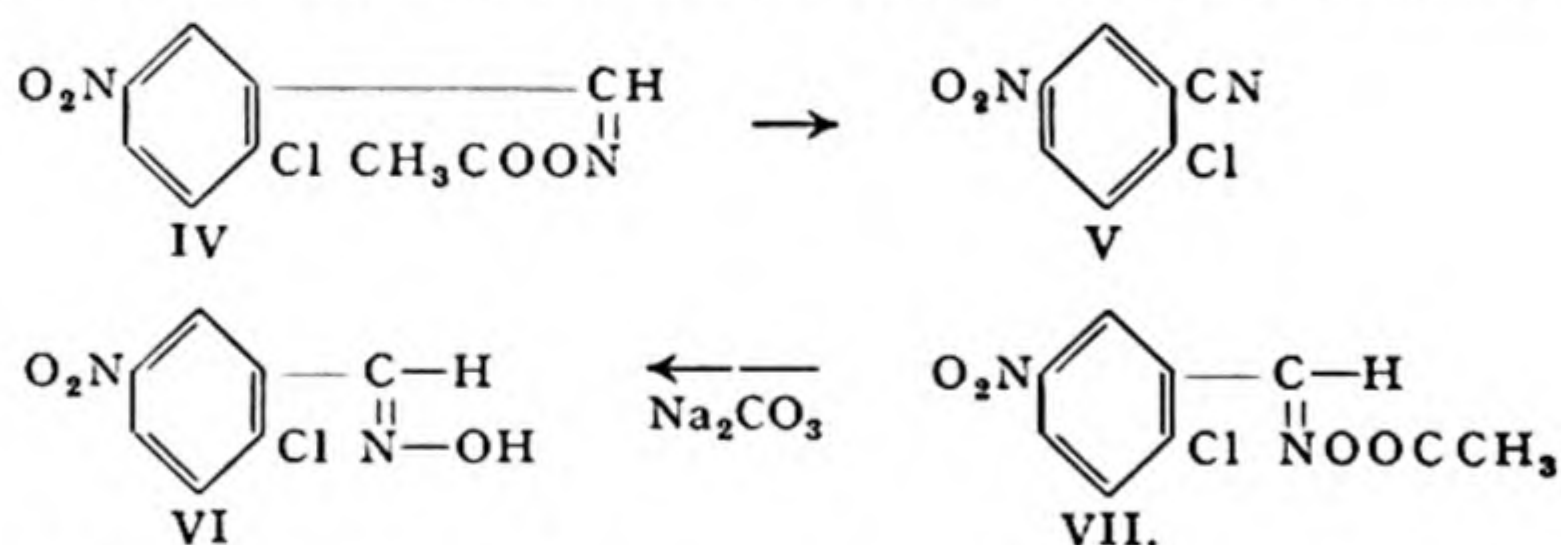
For determining the configuration of the two stereoisomers, initially a method given by HANTZSCH was used. By treatment with acetic anhydride at ordinary temperature

both forms of benzaldoxime gave an acetyl compound. One of the acetyl compounds was converted into *benzonitrile* C_6H_5CN , on treatment with dilute alkali, acetic acid being split off as sodium acetate, and was therefore assigned the *syn*-configuration, because it was assumed that the groups H and CH_3COO^- would easily form acetic acid when in the *cis*-position to one another. Benzaldoxime was reproduced when the other acetyl compound was treated with dilute alkali, therefore it was assigned the *anti*-configuration.

From the following example it would appear that this method of determining configuration may lead to erroneous conclusions (BRADY; MEISENHEIMER). By the action of hydroxylamine on 2-chloro-5-nitrobenzaldehyde, a 2-chloro-5-nitrobenzaldoxime melting at 152° is obtained. This " α -form" is partially converted into the " β -form" melting at 172° by the action of hydrogen chloride in ethereal solution. This reaction is reversible. The β -form is not formed by the action of hydroxylamine on 2-chloro-5-nitrobenzaldehyde and hydrogen chloride is very easily eliminated from it by the action of dilute alkali, with the production of an isoxazole derivative II, which passes over into the isomeric 2-hydroxy-5-nitrobenzonitrile:

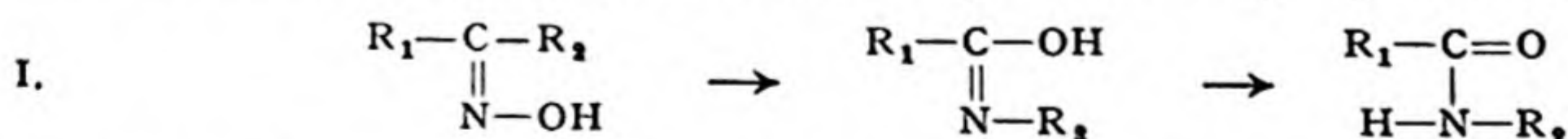


On these grounds the *anti*-configuration I is assigned to the β -form, which gives an acetyl compound IV on treatment with acetic anhydride, from which, in its turn 2-chloro-5-nitrobenzonitrile V is produced by the action of dilute alkali. Thus the H- and CH_3COO^- groups situated in the *trans*-position are split off as acetic acid:

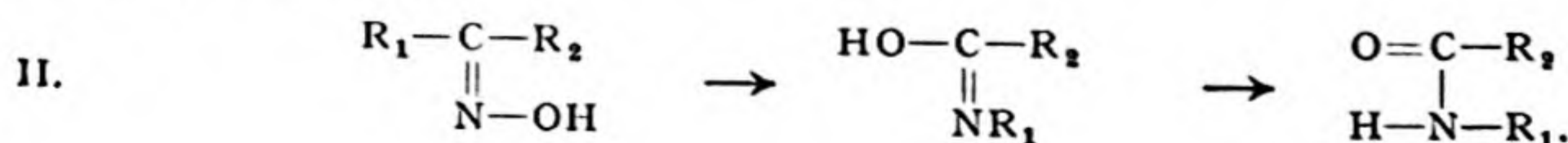


The α -form of 2-chloro-5-nitrobenzaldoxime is unattacked by dilute alkali or is attacked extremely slowly; this form therefore has the *syn*-configuration VI. The α -oxime can be recovered from its acetyl derivative VII by the action of soda solution at ordinary temperatures; hence the H- and CH_3COO^- groups are not split off as acetic acid.

In the BECKMANN transformation of ketoximes (59), it appears, in many cases, that the reaction does not take place in such a way that the *cis*-groups interchange (scheme I):



but a transformation occurs in which groups situated in the *trans*-position exchange places (scheme II):

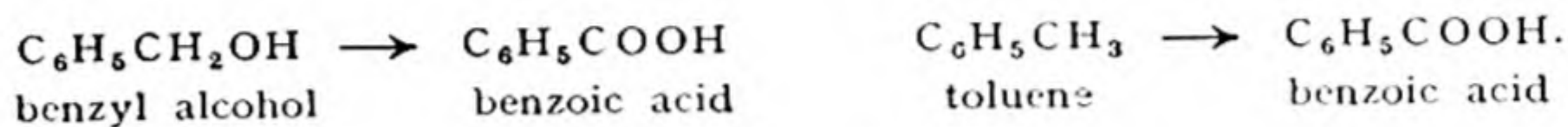


(xiii) AROMATIC CARBOXYLIC ACIDS AND THEIR DERIVATIVES

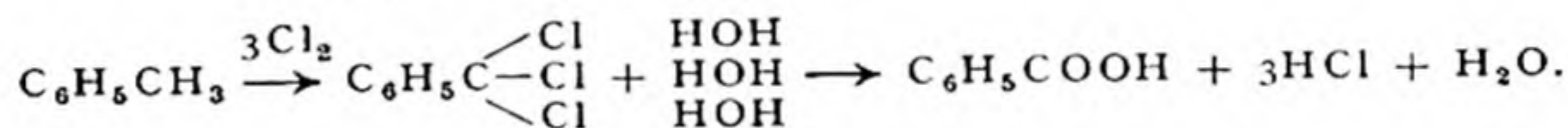
Mono-carboxylic acids of benzene and its homologues

260. *Benzene carboxylic acid* or *benzoic acid* C_6H_5COOH , is the simplest aromatic acid. It occurs in small quantities in gum benzoin, which also contains 12-18 % of esters of benzoic acid, in tolu- and Peru-balsams. Benzoic acid was isolated from gum benzoin as early as 1755 by SCHEELE and was more closely investigated by LIEBIG and WÖHLER and by MITSCHERLICH in 1832. It may be prepared in various ways as follows:

1. By the oxidation of benzene derivatives with one side-chain like toluene, ethylbenzene, benzyl alcohol, phenylethyl alcohol, etc:



Technically, benzoic acid is prepared by passing chlorine into boiling toluene to produce phenyltrichloromethane (benzotrichloride) $C_6H_5CCl_3$, which is converted into benzoic acid by boiling with water; a little chlorobenzoic acid $C_6H_4\begin{Bmatrix} Cl \\ COOH \end{Bmatrix}$, is produced at the same time:



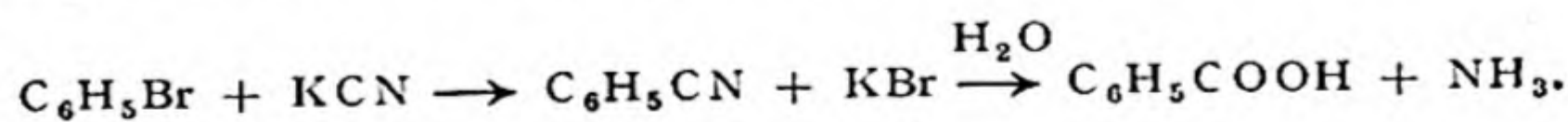
At the present time benzoic acid is made on a commercial scale also from phthalic anhydride (266), which is mixed with steam and passed over zinc oxide at 450° when it is split up into carbon dioxide and benzoic acid, the zinc oxide acting catalytically.

2. By the hydrolysis of benzene carbonitrile:



3. By allowing dry carbon dioxide to react with phenylmagnesium bromide and decomposing the addition product with water (66).

4. By heating bromobenzene with an aqueous alcoholic solution of potassium and copper cyanides to 200° . Benzenecarbonitrile is formed as an intermediate product, which is hydrolysed directly to benzoic acid:



Benzoic acid crystallises in colourless leaflets or needles melting at 121.4° . It is sparingly soluble in water and more readily soluble in alcohol and ether. It is volatile in steam and may be sublimed; it boils at 250° . The

dissociation constant of benzoic acid is $k = 0.6 \times 10^{-4}$; hence it is a stronger acid than acetic acid (68).

Benzoic acid is used for the synthesis of anthraquinone dyestuffs, (283) as well as for other purposes. Sodium benzoate is used as a food preservative since it has antiseptic properties like the free acid and is relatively non-toxic.

The solubility curve for benzoic acid in water is given in Fig. 64. The solubility rises fairly rapidly with the temperature to 94° (branch AB). At this temperature the acid melts under water so that two liquid layers are formed, an aqueous layer containing 11.2 % of acid and an acid layer containing 95.9 % of acid.

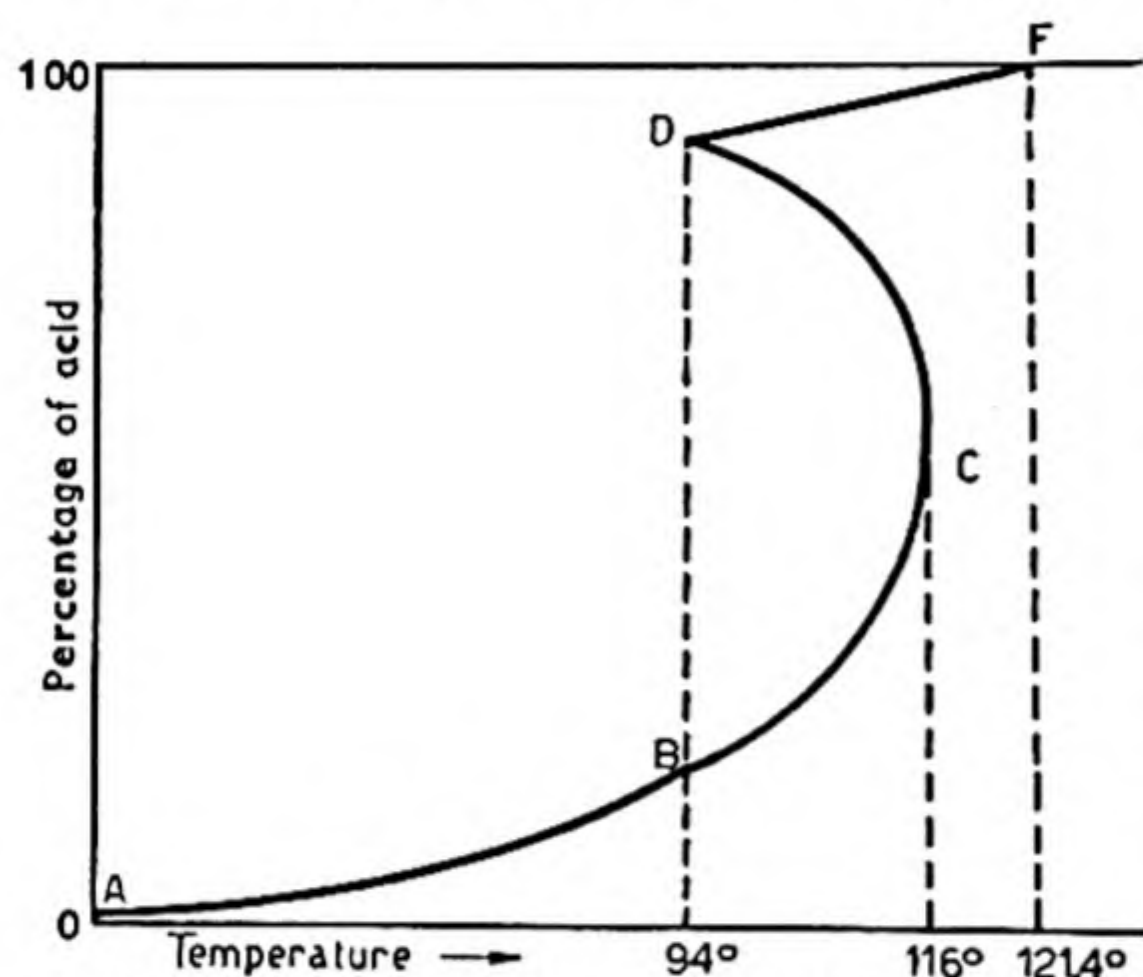
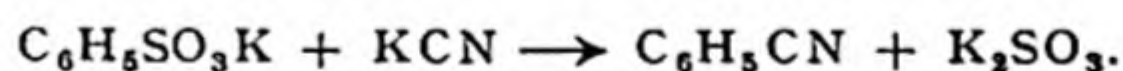


Fig. 64. Solubility curve for benzoic acid in water

As the temperature is increased, both the solubility of benzoic acid in water and that of water in benzoic acid increases. This is represented by the portion of the curve BCD, in which BC represents the composition of the aqueous layer and DC that of the acid layer. The composition of both layers approach one another as the temperature is raised still further, and at 116° they are identical. At this temperature the liquid becomes homogeneous. If more benzoic acid is added to the acid-rich layer above 94° , the temperature must be increased to maintain the whole mass molten, the part of the curve then traversed is DF, which ends at F the melting point of pure benzoic acid. The line DF represents the melting point curve of the acid on the addition of water.

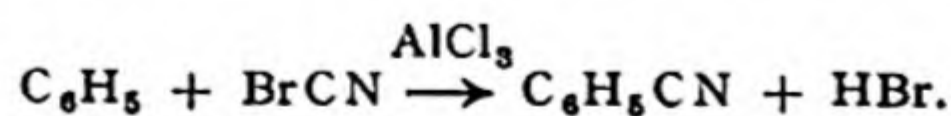
Benzenecarbonitrile or *benzonitrile* is the simplest example of an aromatic carbonitrile. Besides being prepared by some of the methods used for the preparation of aliphatic carbonitriles, such as by the action of phosphorus pentoxide on aromatic carbonamides, these compounds can be prepared by the methods given below:

1. By heating the potassium salt of an aromatic sulphonic acid with potassium cyanide or potassium ferrocyanide:



2. By treating a diazonium salt with potassium copper cyanate (155).

3. By the action of cyanogen bromide on aromatic hydrocarbons—or on aryl ethers—in the presence of aluminium chloride:

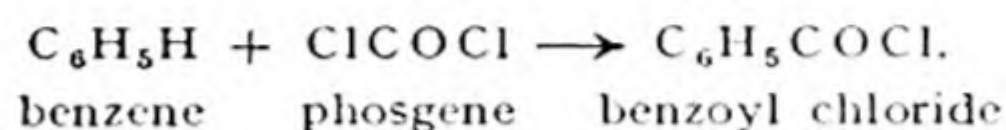


The CN-group in aromatic carbonitriles shows the same properties as in the aliphatic carbonitriles. On treatment with sodium in boiling alcohol,

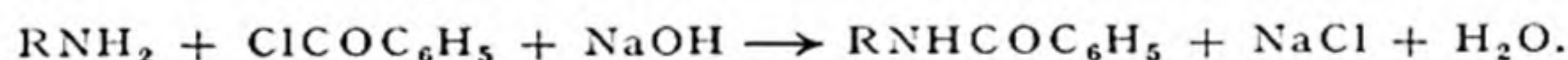
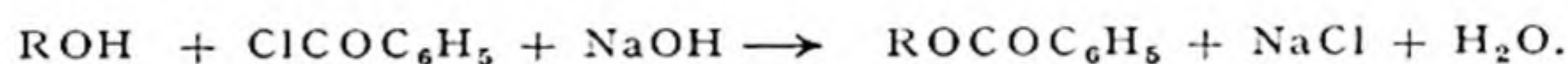
benzonitrile is partly reduced to benzylamine and partly hydrolysed to benzoic acid. Aromatic carbonitriles can be converted into aldehydes by the method of STEPHENS (58).

Benzonitrile is a liquid boiling at 191° and possessing an odour of bitter almonds.

Benzenecarbonyl chloride or *benzoyl chloride* C_6H_5COCl , is an unpleasant smelling liquid with m.p. -1° and b.p. 198° . Benzoyl chloride is produced by the action of carbonyl chloride on benzene in the presence of aluminium chloride:

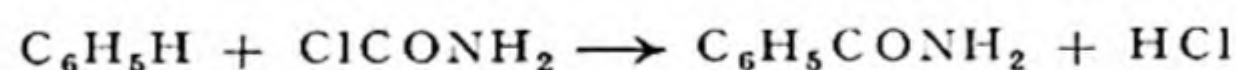


It is prepared commercially by chlorinating benzaldehyde. Benzoyl chloride is more stable than acetyl chloride towards water and is hydrolysed to benzoic and hydrochloric acids only very slowly by cold water. Consequently it can be used as a benzoylating agent in aqueous media and is therefore an important reagent for introducing the benzoyl radical into hydroxy- and amino-compounds. To this end the substance to be benzoylated is shaken with benzoyl chloride in a strongly alkaline solution; the benzoyl derivative separates and the excess benzoyl chloride passes into solution as sodium benzoate (SCHOTTEN-BAUMANN method):



Benzoylations are frequently carried out also in anhydrous media (*e.g.* pyridine, benzene, etc.).

Benzamide $C_6H_5CONH_2$, m.p. 130° , is produced from carbamyl chloride, benzene and aluminium chloride:



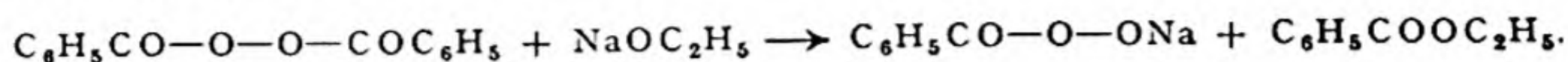
or from benzoyl chloride and ammonium carbonate or ammonia. The hydrogen atoms in the amino-group are more easily replaced by metals than in acetamide (78), since benzoic acid is a stronger acid than acetic acid.

Benzoic anhydride $C_6H_5CO-O-COC_6H_5$, is produced by boiling benzoic acid with acetic anhydride.

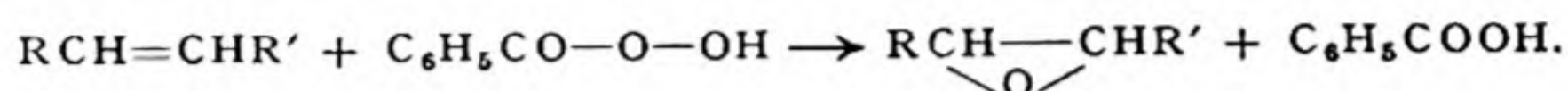
Methyl and ethyl benzoates. Aromatic carboxylic acids are esterified in the same way as aliphatic acids. The methyl ester of benzoic acid $C_6H_5COOCH_3$, is a liquid boiling at 198° , which finds a use in the perfumery industry.

Benzoyl peroxide $C_6H_5CO-O-O-COC_6H_5$, is produced by the action of benzoyl chloride on hydrogen peroxide in alkaline solution. It melts at 103° , acts as an oxidising agent and is used as a bleaching agent, *e.g.* for flour.

Perbenzoic acid $\text{C}_6\text{H}_5\text{CO}-\text{O}-\text{OH}$, is an example of an organic peracid. It melts at $41-43^\circ$ but decomposes on heating. The sodium salt of this acid is prepared by allowing sodium ethylate to react with benzoyl peroxide:



Perbenzoic acid oxidises compounds containing a double bond by adding an atom of oxygen with the formation of a derivative of ethene oxide, thus:



Substituted benzoic acids

261. *Halogenobenzoic acids.* *m*-Chlorobenzoic acid $\text{C}_6\text{H}_4\text{Cl}(\text{COOH})$, is the main product formed along with more highly chlorinated acids (which are difficult to separate from one another) by chlorinating benzoic acid in the presence of ferric chloride as a catalyst. *o*-, *m*- and *p*-Chlorobenzoic acids can be prepared from the corresponding amino-compounds via the diazonium chlorides. *p*-Chloro- and *p*-bromo-benzoic acids are usually obtained by oxidising the corresponding halogeno-toluenes (**221**). Substitution of benzoic acid by chlorine increases its acid character, to the greatest extent in the *ortho*-compound and least in the *para*-compound.

TABLE 48

SOME PHYSICAL CONSTANTS OF BENZOIC ACID AND ITS MONO-CHLORO- AND MONO-NITRO- DERIVATIVES

	M.p.	Dissociation const. <i>k</i>		M.p.	Dissociation const. <i>k</i>
Benzoic acid	121°	0.00006			
<i>o</i> -Chlorobenzoic acid	138°	0.00136	<i>o</i> -Nitrobenzoic acid	148°	0.00620
<i>m</i> -Chlorobenzoic acid	153°	0.00015	<i>m</i> -Nitrobenzoic acid	141°	0.000345
<i>p</i> -Chlorobenzoic acid	234°	0.000093	<i>p</i> -Nitrobenzoic acid	241°	0.00041

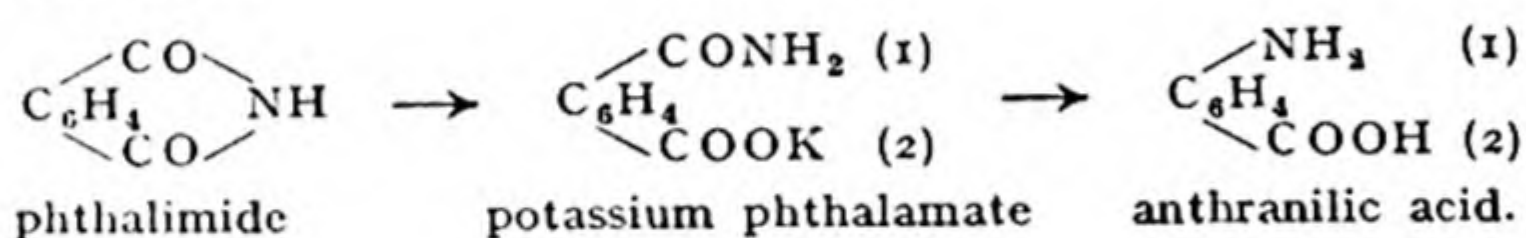
Nitrobenzoic acids $\text{C}_6\text{H}_4(\text{NO}_2)\text{COOH}$. *m*-Nitrobenzoic acid is the main product along with about 20 % of the *ortho*-acid and a small amount of the *para*-isomer, produced in the nitration of benzoic acid with anhydrous nitric acid. *o*- and *p*-Nitrobenzoic acids can be prepared by oxidation of the corresponding nitrotoluenes. From Table 48 it will be seen that the nitrobenzoic acids are stronger acids than benzoic acid.

Sulphobenzoic acids. *m*-Sulphobenzoic acid (90 %) and about 10 % of the *para*-compound are produced in the sulphonation of benzoic acid with fuming sulphuric acid.

The imide of *o*-sulphobenzoic acid is *saccharin*, a substance discovered in

In recent investigations by VERKADE it has been found that *2-amino-4-nitro-n-propoxybenzene*, $\text{O}_2\text{N}-\text{C}_6\text{H}_2(\text{NH}_2)\text{OC}_3\text{H}_7$, is about 4000 times sweeter than cane-sugar so that this substance can be used as a substitute for sugar notwithstanding its low solubility in water. The above mentioned "sweetening agents" have nothing in common structurally with the saccharides (159).

262. *Aminobenzoic acids* $\text{C}_6\text{H}_4(\text{NH}_2)\text{COOH}$. The *ortho*-derivative, *anthranilic acid*, is the most important; it has all the characteristics of an amino-acid, giving salts with both acids and bases. Anthranilic acid was obtained in 1841 by FRITZSCHE as an oxidation product of indigo (316). It may be obtained from phthalimide (266) and sodium hypobromite or bleaching powder by the method of HOOGEWERFF and VAN DORP (78). In this process, the salt of phthalamic acid (the mono-amide of phthalic acid) is formed as an intermediate product, which is converted into *o*-aminobenzoic acid by a HOFMANN reaction:



Anthranilic acid melts at 145° , can be sublimed without decomposition, is readily soluble in water and alcohol, and has a sweet taste and weak anti-septic properties. It is used in the preparation of some dyestuffs (see for example, 253).

The methyl ester of this acid has an intense flower-like scent and occurs in essential oils, *e.g.* oil of jasmine.

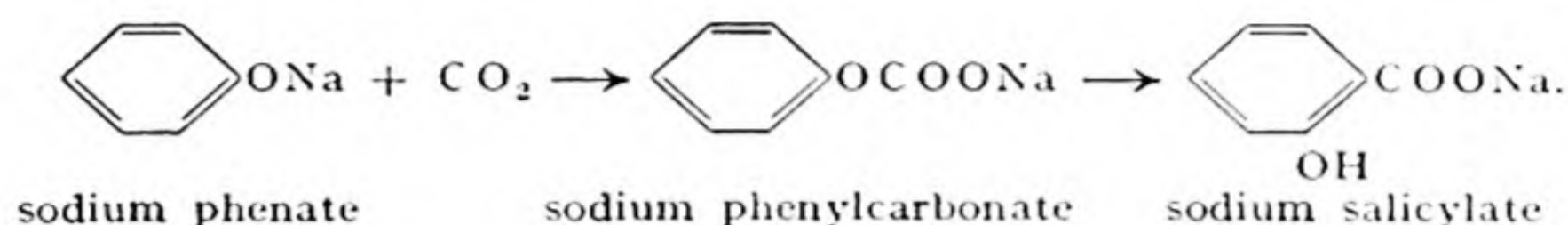
p-Aminobenzoic acid (m.p. 187°) is of importance for the preparation of substances with local anaesthetic action, *e.g.* *novocaine*, which is the hydrochloride of *diethyl-aminoethyl p-aminobenzoate*:



263. *Mono-hydroxybenzoic acids* $\text{C}_6\text{H}_4(\text{OH})\text{COOH}$. *o*-Hydroxybenzoic acid or *salicylic acid*, $\text{C}_6\text{H}_4 \begin{array}{c} \text{OH} \text{ (1)} \\ \diagup \quad \diagdown \\ \text{COOH} \text{ (2)} \end{array}$, is the most important compound in this group. The name is derived from *salicoside* (256). Methyl salicylate, which is of some importance as a perfume, occurs in oil of wintergreen.

Salicylic acid was discovered by PIRIA in 1838 and was at one time produced by oxidising saligenin (256) but at the present time it is prepared commercially by SCHMIDT's modification of the KOLBE method (1874), in which carbon dioxide under pressure is allowed to interact with sodium phenate at 130° .

At ordinary temperature and a pressure of about one and a half atmospheres, sodium phenylcarbonate is produced, to which is assigned the formula given below, since it is decomposed by dilute acids into phenol, carbon dioxide and a sodium salt of the acid employed, *e.g.* sodium chloride. This sodium phenylcarbonate may be regarded as an intermediate product in the formation of sodium salicylate:

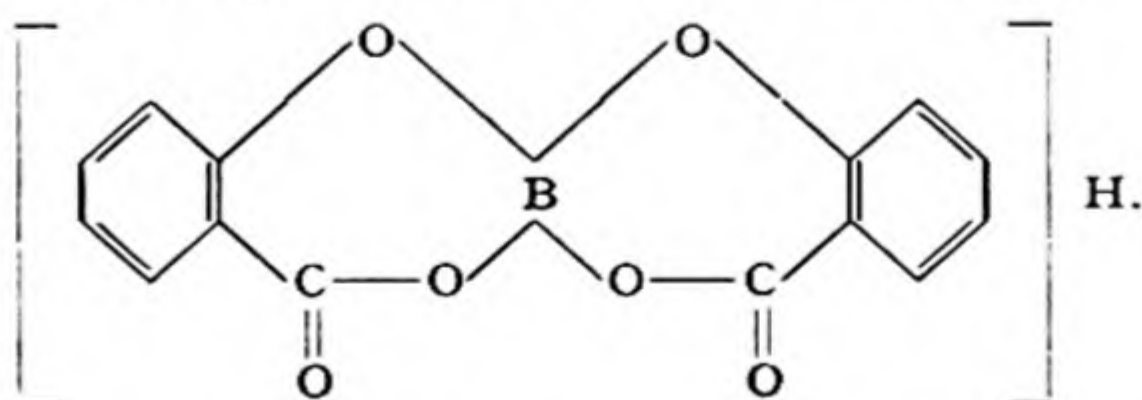


Salicylic acid can also be obtained by the oxidation of *o*-cresol (230) with potassium hydroxide and lead peroxide, by treating anthranilic acid (262) with nitrous acid or by fusing *o*-chloro- or *o*-bromo-benzoic acid with potash.

Salicylic acid (m.p. 159°) is difficultly soluble in cold water; it is a stronger acid than benzoic acid ($k = 1.06 \times 10^{-3}$). It can be sublimed by careful heating but it decomposes into phenol and carbon dioxide at higher temperatures. With bromine water it gives a precipitate, having the structure $\text{C}_6\text{H}_2\text{Br}_3\text{OBr}$. With ferric chloride in alcoholic solution, salicylic acid gives an intense violet colour. (Phenol is not coloured violet in alcoholic solution by ferric chloride.)

Salicylic acid is used in the preparation of azo-dyestuffs (253). Since the acid is a powerful antiseptic and disinfectant, it is used for preserving foodstuffs. Many derivatives of salicylic acid are used as drugs, like the sodium salt and the acetyl compound, $\text{C}_6\text{H}_4 \begin{array}{l} \text{OCOCH}_3 \text{ (1)} \\ \text{COOH} \text{ (2)} \end{array}$, (m.p. 135°), known under the name of *aspirin* and the phenyl ester, *salol*, $\text{C}_6\text{H}_4 \begin{array}{l} \text{OH} \\ \text{COOC}_6\text{H}_5 \end{array}$, which is prepared by warming salicylic acid with phenol and phosphorus oxychloride.

With boric acid, salicylic acid gives a complex compound, *borosalicylic acid*, which has been resolved into optically active forms (BÖESEKEN):



From this it follows, that the substituents around the coordinative tetravalent boron atom are arranged tetrahedrally, making two mirror-image forms possible. This is an example of molecular asymmetry (37, 92).

m-Hydroxybenzoic acid melts at 188° and does not give a colour reaction with ferric chloride. It is prepared on a technical scale by fusing *m*-sulphobenzoic acid (261) with potash and is used in the manufacture of some dyestuffs.

p-Hydroxybenzoic acid melts at 213° and also fails to give a colour reaction with ferric chloride.

Dihydroxybenzene carboxylic acids $C_6H_3(OH)_2COOH$. Of these, *protocatechuic acid* $H_3C_6 \begin{matrix} \swarrow COOH (1) \\ \searrow OH (3) \\ \swarrow OH (4) \end{matrix}$ is the most important. It occurs in the free state in the fruits of *illicium religiosum* and is produced by fusing various kinds of natural resins with potash and from catechol (232) by heating it under pressure to 140° with a solution of ammonium carbonate. This is a striking example of the easy introduction of the carboxyl group into the benzene nucleus.

Protocatechuic acid is readily soluble in water and melts at 195° . It reduces ammoniacal silver solution but not an alkaline solution of a copper salt.

Trihydroxybenzoic acids $C_6H_2(OH)_3COOH$. The most important acid of this group is *gallic acid* $H_4C_6 \begin{matrix} \swarrow COOH (1) \\ \searrow OH (3) \\ \swarrow OH (4) \\ \searrow OH (5) \end{matrix}$, which is very widely distributed throughout the vegetable kingdom occurring, for example, in galls (oak-apples), tea and oak bark. The commercial preparation of gallic acid depends on the hydrolysis of aqueous extracts of galls by either dilute acids or by moulds (*Penicillium glaucum*, *Aspergillus niger*). These moulds contain an enzyme *tannase*, which breaks down tannins (264) into glucose and gallic acid.

Gallic acid melts at 222° and is readily soluble in hot water. On heating, it breaks down into carbon dioxide and pyrogallol (232), from which it follows that the three phenolic hydroxyl groups are situated next to one another. It reduces gold and silver salts and gives a blue-black precipitate with ferric chloride. In alkaline solution it becomes brown in colour due to oxidation by air.

Writing ink consists mainly of an aqueous solution of gallic acid and ferrous sulphate, gum arabic and a little sulphuric acid, the addition of the latter serving to retard oxidation of the ferrous sulphate by air. When the solution is spread out on paper, however, the siliceous earths, which are always present in the latter, neutralise the sulphuric acid. The ferrous sulphate is then rapidly oxidised to ferric sulphate, which forms a deep black precipitate with the gallic acid. Hence the writing when dry is an intense black. Since the mixture of ferrous sulphate and gallic acid solutions is pale brown in colour, indigo-carmin or some other blue dye is added so that the ink is deep blue in colour as it flows from the pen.

Toluene carboxylic acids, toluidic acids or methylbenzoic acids, $C_6H_4(CH_3)COOH$, can be made by partial oxidation of the isomeric xylenes, or more satisfactorily, from the corresponding toluidines by converting them via the diazonium salts into the nitriles, which are hydrolysed to the correspond-

ing acids. On oxidation the toluic acids give the dibasic phthalic acids (266).

The *xylic acids* $C_6H_3(CH_3)_2COOH$, are obtained in a similar way from the xylicidines. Both the toluic and the xylic acids are solid substances, which are sparingly soluble in water.

264. *Tannins* are compounds possessing the property of converting animal skin into leather. They precipitate proteins from their solutions and also give precipitates with alkaloids. They are soluble in water giving solutions, which give dark blue or green precipitates with ferric salts; they have a bitter, astringent taste. The tannins, which occur widely distributed throughout the vegetable kingdom, are divided into two main groups.

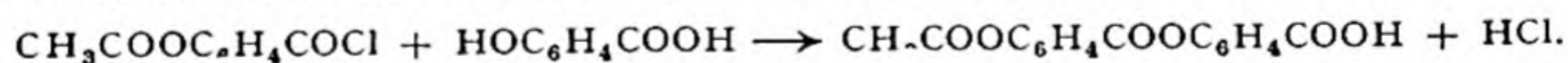
1. A few tannins, which may be regarded as hydrolysable esters. To these belong *tannin* (or *tannol*), which occurs in galls and is a derivative of gallic acid.

2. A large group of tannins, including the tannin from oak bark, which are related to *catechin*, a colourless, crystalline substance forming the chief constituent of *gambir*, a tannin from Sumatra. It is related in structure to the *flavonols* (328) and *anthocyanins* (331).

Closely related with tannin is a group of compounds called *depsides* (from the Greek verb $\delta\epsilon\psi\epsilon\iota\omega$ = to tan) by E. FISCHER, to denote ester-like compounds derived from aromatic hydroxy-acids.

An example of a depside is the didepside from *p*-hydroxybenzoic acid, $HOC_6H_4COOC_6H_4COOH$, in which the carboxyl group in one molecule of hydroxybenzoic acid is esterified by the phenolic hydroxyl group in a second molecule of acid.

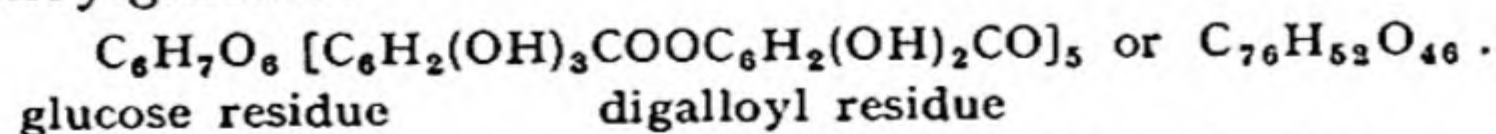
For the synthesis of the depsides, E. FISCHER starts from an acetyl derivative of a hydroxy-acid, which is converted into the acid chloride; the latter is then treated in benzene solution with hydroxybenzoic acid and dimethylaniline, when hydrogen chloride is eliminated and combines with the added base:



The acetyl residue is split off from the acetyl derivative of the depside by methanolic hydrochloric acid.

In a similar way, tri-, tetra- and poly-depsides were built up in which three, four or more aromatic hydroxy-acids, respectively, were present. Depsides occur in nature as constituents of lichens.

Tannins are split up into glucose and gallic acid by warming with dilute sulphuric acid, about ten molecules of gallic acid being produced for very molecule of glucose. E. FISCHER synthesised a *pentadigalloylglucose*, which showed great similarity to tannin in its properties. He first of all made a didepside *galloylgallic acid*, $C_6H_2(OH)_3COOC_6H_2(OH)_2COOH$, from gallic acid and he reacted its chloride with glucose to form pentadigalloylglucose:

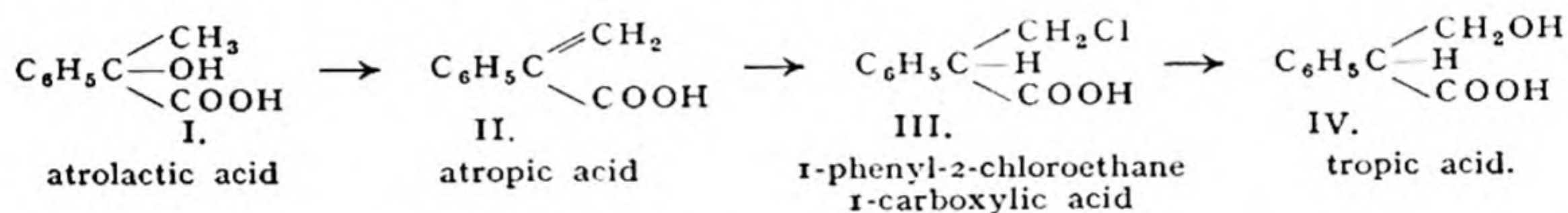


Tannin consists of a mixture of digalloyl derivatives of glucose.

Inactive *dl*-mandelonitrile is produced in this synthesis. Under the influence of emulsinase (208), however, this synthesis takes such a course that *l*-mandelonitrile is produced in excess (ROSENTHALER). For asymmetric synthesis with quinine and quinidine as catalysts see 209.

Natural mandelic acid is laevo-rotatory. The synthetic acid can be resolved into its components via the cinchonine salts. *dl*-Mandelic acid melts at 119° and is readily soluble in water; the active forms, $\alpha_D = 157^{\circ}$, melt at 134° and are less soluble in water. Mandelic acid is used in medicine as an internal disinfectant.

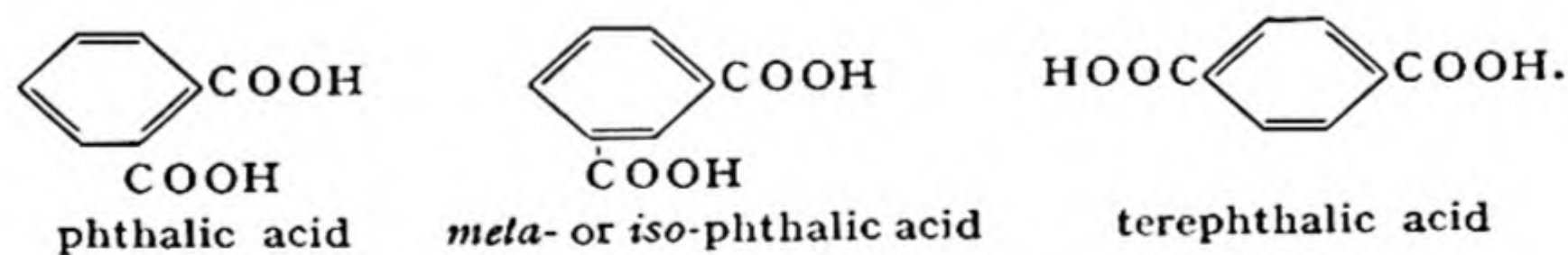
Tropic acid or *1-phenyl-2-hydroxyethane 1-carboxylic acid*, a fission product of atropine and hyoscyamine (357) can be prepared synthetically in the following way. From acetophenone and hydrocyanic acid followed by hydrolysis of the resultant nitrile, there is produced *atrolactic acid* (I), which loses a molecule of water on dry distillation giving *1-phenylethene 1-carboxylic acid* or *atropic acid* (II), which will, in its turn, add on a molecule of hydrogen chloride (III) and produce *tropic acid* (IV) on boiling the product with dilute soda solution:



The inactive acid melts at 117° , the optically active forms at 127° . The optically active forms are produced by resolving the *dl*-acid through the quinine salts.

Dicarboxylic acids of benzene and its homologues

266. Benzene dicarboxylic acids $\text{C}_6\text{H}_4(\text{COOH})_2$. Of the three isomers, the *ortho*-dicarboxylic acid, *phthalic acid*, is the most important. It was discovered in 1836 by LAURENT as an oxidation product of naphthalene (279):



Phthalic acid is produced by oxidising aromatic hydrocarbons with two side-chains in *ortho*-positions, with potassium permanganate; it was first of all prepared commercially from naphthalene by oxidation with fuming sulphuric acid and mercuric sulphate as a catalyst. In a more recent process, naphthalene vapour is oxidised with air at $400\text{--}500^{\circ}$ in the presence of vanadium pentoxide as a contact material to give phthalic anhydride (WOHL; GIBBS).

The dissociation constant of phthalic acid is 1.26×10^{-3} , it is therefore

However, a higher molecular refraction is to be expected for a compound of structure I than for one of structure II, because chlorine atoms attached directly to a $>C=O$ group would contribute a greater amount to the molecular refraction than chlorine atoms attached to a carbon atom not carrying a doubly bound oxygen atom.

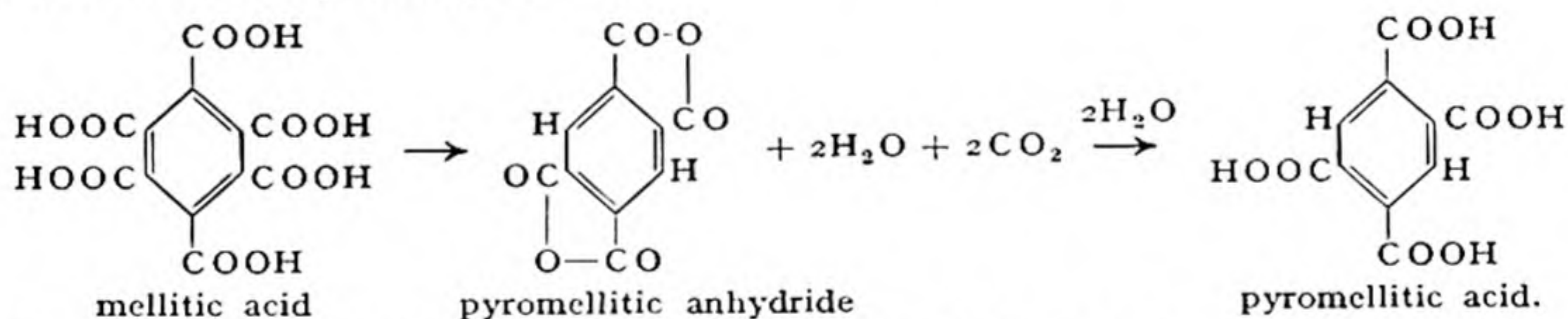
Also, the atomic refraction for an oxygen atom in a carbonyl group, is greater than for an atom of oxygen attached to two separate carbon atoms. The form melting at 16° has a molecular refraction which is rather larger than the calculated value based on structure I; therefore this latter structure is assigned to this form.

Meta- or iso-phthalic acid is produced by oxidising *m*-xylene with dilute nitric acid. It is difficultly soluble in water, does not form an anhydride and melts at 348° . It sublimes without decomposition.

Terephthalic acid, benzene 1,4-dicarboxylic acid, is produced by oxidising *p*-toluic acid or turpentine. It is practically insoluble in water, alcohol and ether. It sublimes without melting at above 300° and does not form an anhydride.

Benzene tri-, tetra- and penta-carboxylic acids are known but are not of much importance.

Benzene hexacarboxylic acid or *mellitic acid*, $C_6(COOH)_6$, is the most important of the higher polybasic benzene carboxylic acids. *Honey stone* or *mellite*, a rare mineral crystallising in honey-yellow, tetragonal crystals found in brown-coal seams, is the aluminium salt of mellitic acid, $C_{12}H_{12}Al_2 + 18H_2O$. Mellitic acid is produced by oxidising charcoal or graphite with fuming nitric acid. Its formation from graphite is in accordance with the view that the carbon atoms in graphite are arranged in hexagonal rings. Mellitic acid is readily soluble in water and alcohol. On heating, it loses two molecules of carbon dioxide and water and is converted into *pyromellitic anhydride*, which forms *pyromellitic acid* by taking up water:

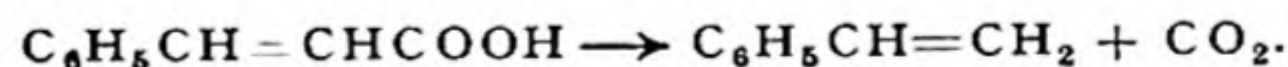


Benzene is produced when mellitic acid is heated with lime.

(xiv) AROMATIC COMPOUNDS WITH UNSATURATED SIDE-CHAINS

Hydrocarbons, alcohols and aldehydes

267. *Phenylethene* or *styrene*, $C_6H_5CH=CH_2$, occurs in storax, a sap from the relative of the plane tree, *Liquidambar orientale*. It can be obtained by slowly distilling cinnamic acid (**268**):

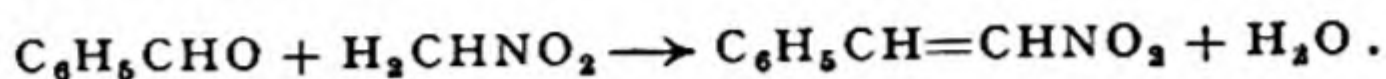


Styrene is prepared on a commercial scale by the catalytic dehydrogenation of ethylbenzene over an aluminium-zinc catalyst at about 600° :

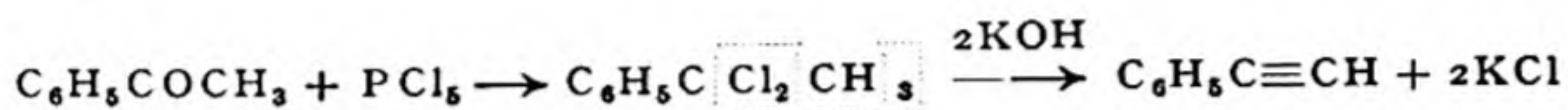


It is a pleasant smelling liquid boiling at 146° and has highly unsaturated properties, which are apparent, for example, from the ease with which it polymerises. By heating or by exposure to sunlight, a glassy mass of *metastyrene* is produced (see **103**).

By treating styrene with nitric acid, *nitrostyrene*, $C_6H_5CH=CHNO_2$, in which the nitro-group is situated in the side-chain, is produced. The structure of this substance follows from its formation by the condensation of benzaldehyde and nitromethane (50) in the presence of alcoholic potash:



Phenylethyne (phenylacetylene) $C_6H_5C\equiv CH$, is produced by the action of phosphorus pentachloride on acetophenone (259) and treatment of the resultant product with alkali:

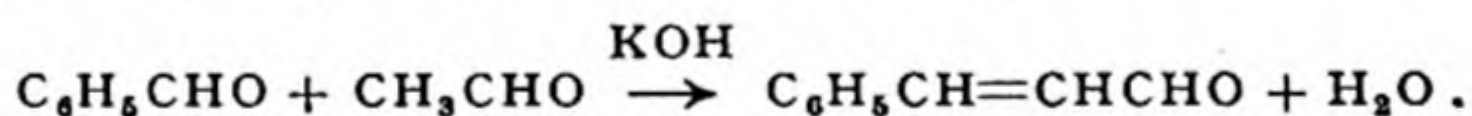


and also by heating the copper salt of phenylethyne carboxylic acids $C_6H_5C\equiv CCOOH$ with water. It is similar to acetylene and gives metal compounds. By dissolving in concentrated sulphuric acid it takes up a molecule of water and is converted into acetophenone.

Unsaturated alcohols. The most important compound in this class is *cinnamyl alcohol* or *3-phenylpropene-2-ol-1*, $C_6H_5CH=CHCH_2OH$, the cinnamyl ester (*styracin*) of which is the main constituent of storax; it occurs in other resins and balsams and has a scent like hyacinths. Cinnamyl alcohol (m.p. 33° , b.p. 257°) is obtained on a commercial scale by hydrolysing storax or by the partial reduction of cinnamaldehyde and is used in the perfumery industry.

Eugenol discussed in 232 is an example of a phenyl ether with an unsaturated side-chain.

Unsaturated aldehydes. *3-Phenylpropenal* or *cinnamaldehyde*, $C_6H_5CH=CHCHO$, the odiferous principle of cinnamon, occurs in many essential oils. It is the main constituent of oil of cinnamon and can be isolated from it by means of its addition compound with sodium bisulphite. It can be prepared synthetically by the condensation of benzaldehyde with acetaldehyde in the presence of dilute alkali:



It is a yellow liquid, boiling with slight decomposition at 252° , which finds a use in the perfumery industry.

Cinnamaldehyde is resinified by strong acids and it forms a compound $N_2(C_6H_5C_3H_3)_3$ with ammonia. In this respect it is similar to benzaldehyde (257).

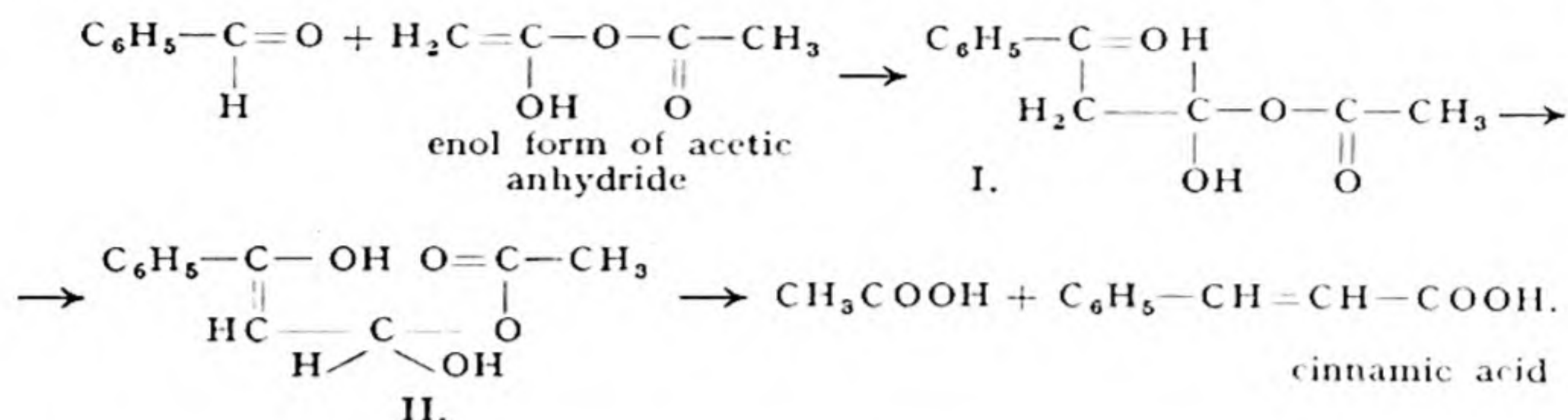
Unsaturated aromatic acids

268. *2-Phenylethene-1-carboxylic acid* or *cinnamic acid*, $C_6H_5CH=CHCOOH$, is the most important member of the group of unsaturated acids. It occurs, partly in the free state but chiefly in the form of esters, in essential oils, and resins, in Peru- and tolu-balsams and in coca leaves.

Technically, cinnamic acid is prepared by the PERKIN synthesis by heating benzaldehyde with acetic anhydride and potassium carbonate.

When other alkaline reacting substances, like tertiary amines, are used instead of potassium carbonate, cinnamic acid is again formed but in lower

yields. It is assumed therefore that acetic anhydride is enolised in the alkaline medium and condenses with benzaldehyde in this form, acetic acid being split off subsequently via the hypothetical intermediates I and II:



A large number of unsaturated acids may be obtained by means of the PERKIN synthesis, since substituted benzaldehydes may be used as well as other acid anhydrides of homologues of acetic acid and of dibasic acids instead of acetic anhydride.

As an unsaturated compound, cinnamic acid forms addition compounds and reduces alkaline permanganate solution.

Cinnamic acid occurs in *cis*- and *trans*-forms:

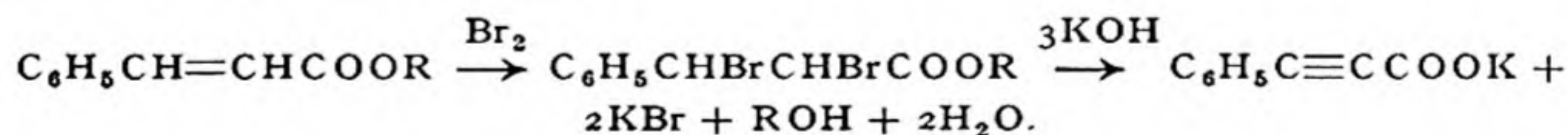


The *cis*-form, which melts at 68° and is called *allo-cinnamic acid*, can be produced by the partial reduction of phenylethyne carboxylic acid, $\text{C}_6\text{H}_5\text{C}\equiv\text{CCOOH}$, with hydrogen in presence of colloidal palladium as catalyst (compare 90).

Allo-cinnamic acid shows trimorphism; two metastable modifications melting respectively at 42° and 58° ("*isocinnamic acids*"), are known. These low melting forms can be converted into the stable modification melting at 68° (BIJLMANN) and can be obtained by the catalytic reduction of phenylethyne carboxylic acid, so that they too also have a *cis*-configuration.

Ordinary cinnamic acid (m.p. 134°) therefore has the *trans*-configuration. *Iso*- and *allo-cinnamic acids* can easily be converted into the stable *trans*-form. Conversely, ordinary cinnamic acid can be converted into the *cis*-form by irradiation with ultra-violet light.

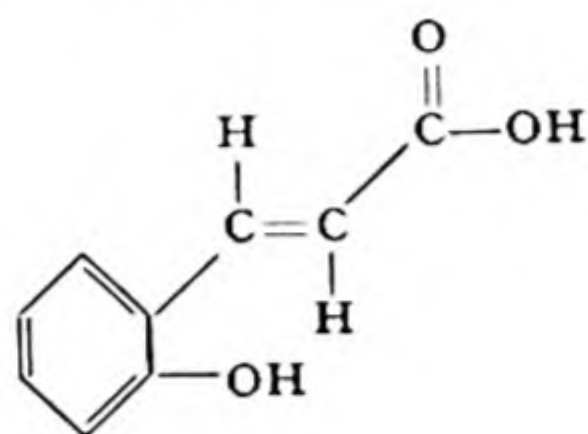
Phenylethyne carboxylic acid or *phenylpropionic acid*, $\text{C}_6\text{H}_5\text{C}\equiv\text{CCOOH}$, (m.p. 136°) is produced from brominated ethyl cinnamate by removing two molecules of hydrogen bromide with alcoholic potash:



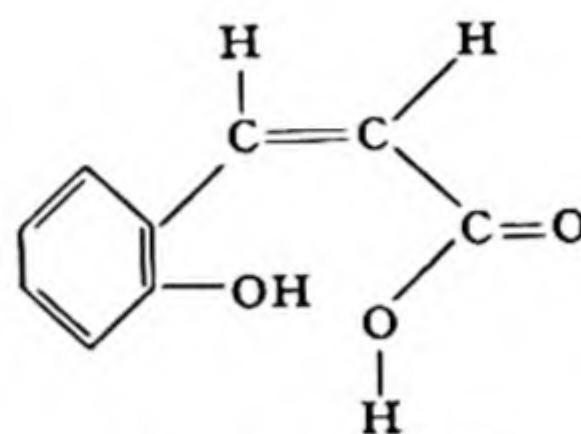
269. Unsaturated mono-hydroxy-acids. *o*-Hydroxycinnamic acid $\text{C}_6\text{H}_4(\text{OH})-\text{CH}=\text{CHCOOH}$ would be expected to exist in two stereoisomeric forms but the acid, *coumaric acid*, is known only in one form in the free state. The

second isomer, *coumarinic acid* is known only in the form of its salts. When attempts are made to liberate the free acid from its salts, a lactone (cf. 130), *coumarin*, (327) is formed. The anhydride corresponding with coumaric acid is not known; when water is extracted from this compound coumarin is produced, which is converted into salts of coumarinic acid by the action of alkaline.

Hence the *trans*-configuration is assigned to coumaric acid and the *cis*-configuration to coumarinic acid:

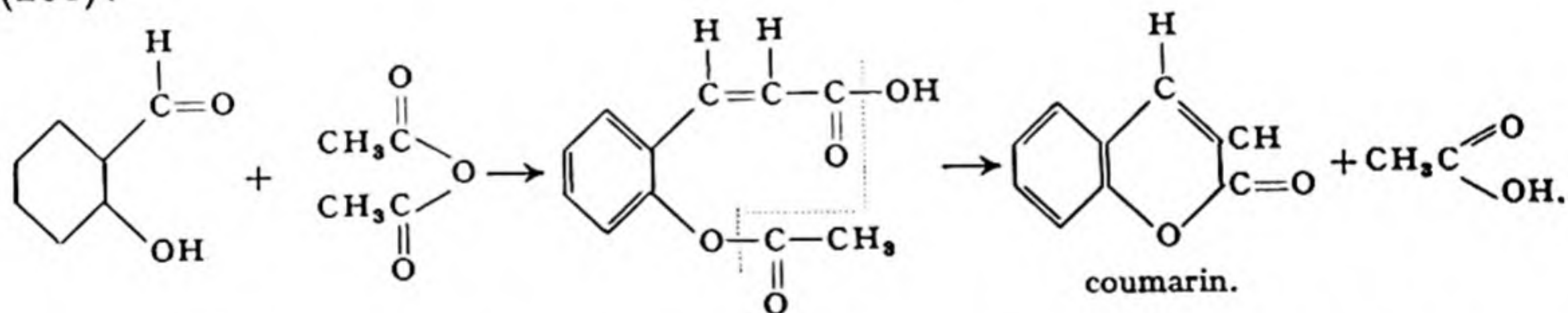


coumaric acid



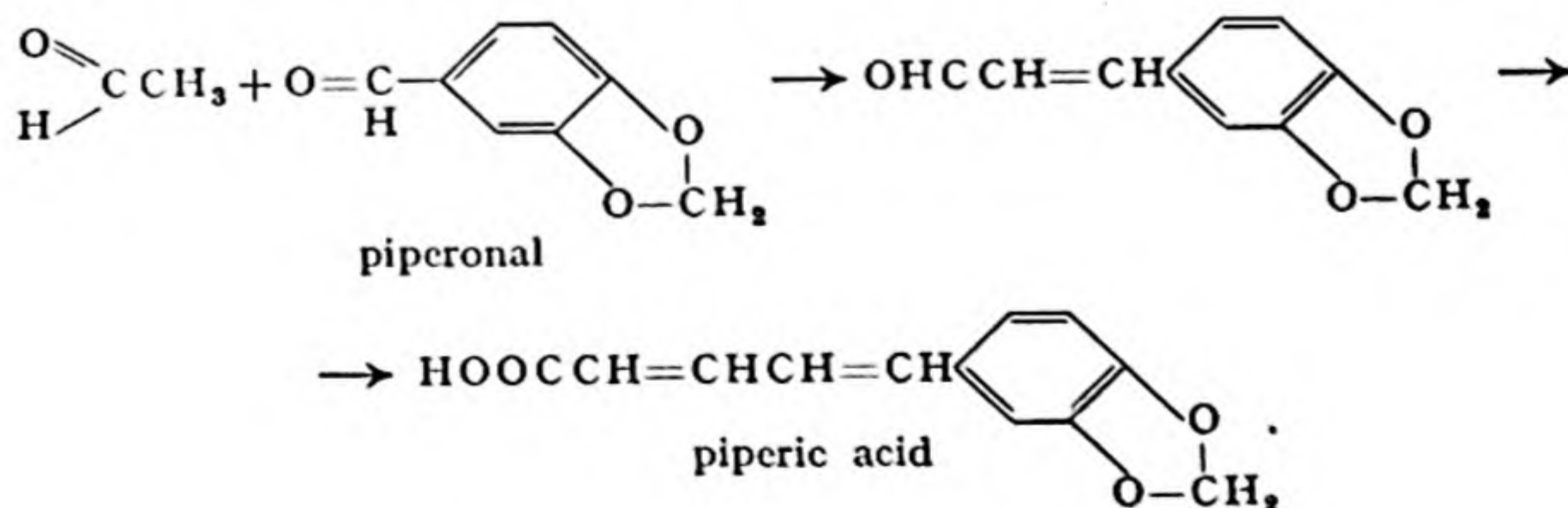
coumarinic acid

Coumarins can be obtained from salicylaldehyde by the PERKIN synthesis (268):



Coumarin is the odiferous substance in woodruff (*asperula odorata*) and occurs also in hay and tonkin beans. Many derivatives of coumarin occur in the vegetable kingdom.

Piperic acid is a fission product of *piperine* (355); it melts at 215° and is very sparingly soluble in water. Its structure follows from the following synthesis: by condensing piperonal (258) with acetaldehyde in an alkaline medium, an unsaturated aldehyde is produced, from which piperic acid is obtained by the action of sodium acetate and acetic anhydride by PERKIN's method:



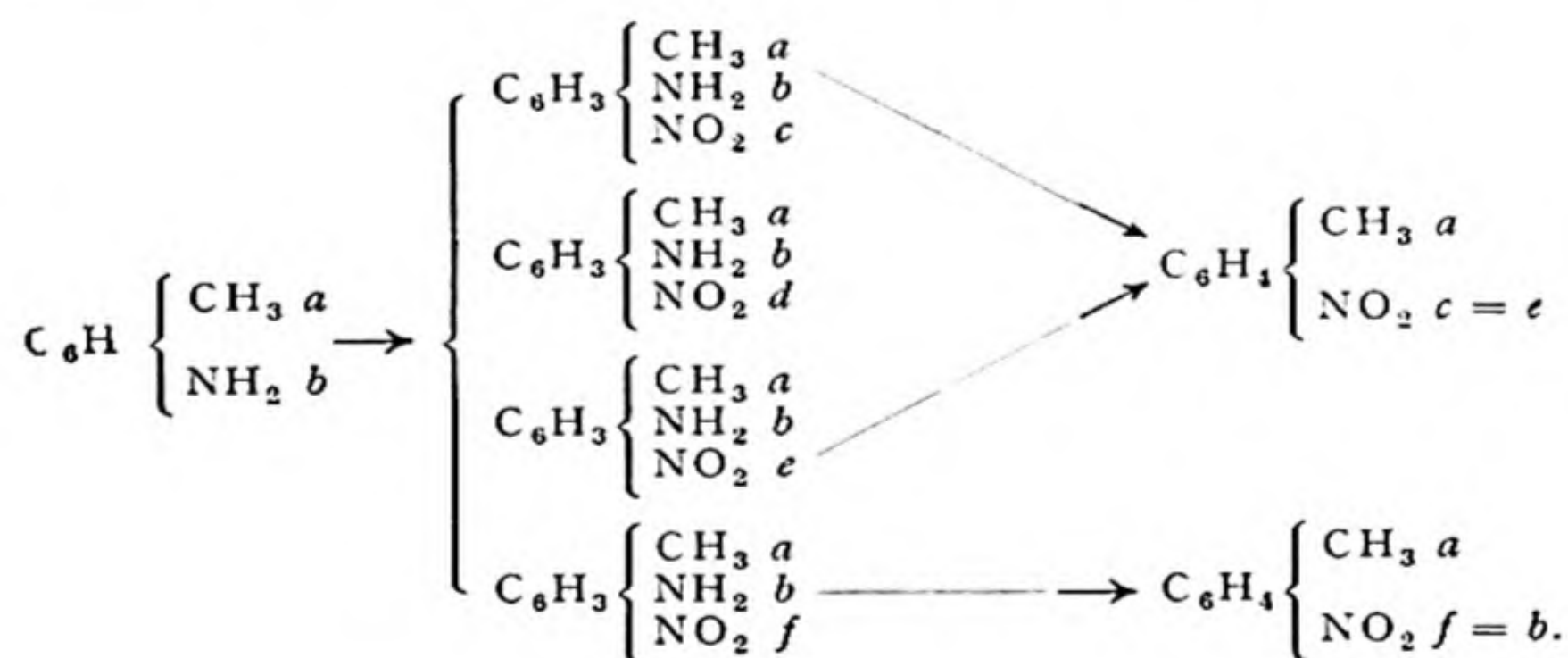
(xv) ORIENTATION OF BENZENE DERIVATIVES

270. The principles on which the orientation of benzene derivatives are based are set out in **217**. A few examples are given below illustrating the application of the theory.

Equivalence of the six hydrogen atoms in benzene. In **214** this equivalence was deduced on the grounds that experience had failed to reveal mono-substitution products of benzene in isomeric forms. Direct proof of this was provided by various investigators (KÖRNER, LADENBURG, NÖLTING) during the years 1869-1876 and the following account is taken from their work.

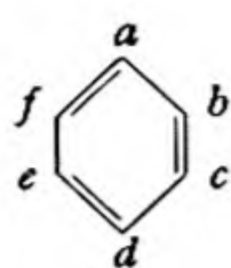
If the six atoms of hydrogen in benzene are denoted by the letters *a*, *b*, *c*, *d*, *e* and *f* and it is assumed arbitrarily, that the amino-group in aniline is situated in position *a*, then, on converting aniline into bromobenzene (via the diazonium compound) and treating this compound with methyl iodide and sodium, toluene will be produced in which the methyl group will also occupy position *a*. On nitrating toluene, three nitrotoluenes are produced (the *meta*-compound in very small amount) in which the nitro-groups may occupy positions *b*, *c* and *d*. On reduction, three toluidines are produced and from these, the amino-group being first of all protected by acetylation, three amino-benzoic acids by oxidation. Carbon dioxide can be split off from these acids with the formation from each isomer of aniline, which is absolutely identical with the starting material, thus proving that $a=b=c=d$.

In order to prove now that *e* and *f* are also equivalent to the other four positions, the starting material is *o*-toluidine, in which the methyl group will be situated in position *a* and the amino-group in position *b*. By nitrating the acetyl compound and subsequent removal of the acetyl group, a mixture of four nitro-*o*-toluidines is obtained:



Since *a* and *b* are already occupied, the nitro-group must occupy positions *c*, *d*, *e* and *f*, respectively, in the four isomers. By replacing the amino-group by hydrogen, four nitrotoluenes are produced with the substituents in positions *ac*, *ad*, *ae* and *af*, respectively. *Ac* and *ad* are obtained in the nitration of toluene and are *m*- and *p*-nitrotoluene; now it is found that *ae* is identical with *ac* and *af* with *ab*. From this it follows that *c* is equivalent to position *e* and position *b* to position *f*.

The same disubstitution product $\text{C}_6\text{H}_4 \left\{ \begin{array}{l} \text{CH}_3 \text{ } a \\ \text{NO}_2 \text{ } c = e \end{array} \right.$ is produced from $\text{C}_6\text{H}_5 \left\{ \begin{array}{l} \text{CH}_3 \text{ } a \\ \text{NH}_2 \text{ } b \\ \text{NO}_2 \text{ } c \end{array} \right.$ and $\text{C}_6\text{H}_5 \left\{ \begin{array}{l} \text{CH}_3 \text{ } a \\ \text{NH}_2 \text{ } b \\ \text{NO}_2 \text{ } e \end{array} \right.$. Hence it is immaterial whether a second substituent enters position *c* or

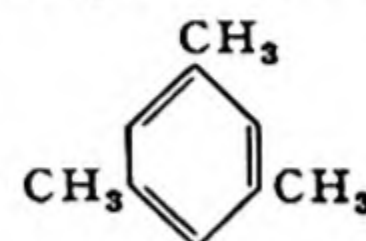


e in a mono-substituted product. Positions c and e are therefore symmetrically situated with regard to a . The same holds for b and f . Consequently, in benzene, there are two pairs of symmetrically situated hydrogen atoms in positions $b=f$ and $c=e$ with respect to a fifth atom of hydrogen in position a .

It is seen that these relationships are clearly expressed in the KÉKULÉ formula.

Absolute orientation

271. *1st. For disubstitution products of benzene.* In a similar way to that just described for benzene, LADENBURG proved in 1876, that the three atoms of hydrogen in the benzene ring of the trimethylbenzene $C_6H_3(CH_3)_3$ boiling at 165° (mesitylene), are equivalent. From this it follows that this compound is, 1,3,5-trimethylbenzene.



Partial oxidation of mesitylene gives 3,5-dimethylbenzoic acid, from which the xylene boiling at 139° is obtained by distillation with lime. Hence this compound has the *meta*-structure.

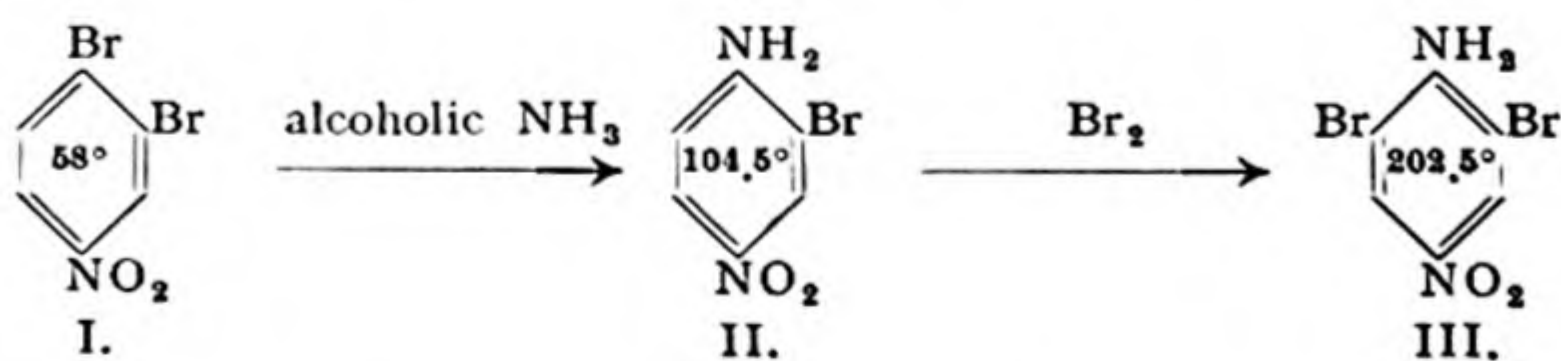
This *m*-xylene on oxidation affords a dicarboxylic acid, *meta*- or *iso*-phthalic acid (**261**), to which the *meta*-configuration must be assigned.

KÖRNER has determined the structure of the three dibromobenzenes, melting at -7° , $+6^\circ$ and 89.3° , respectively, by his method (1874), as already mentioned in **217**.

Two mono-nitrodibromobenzenes, melting at 60.4° and 82.6° , are obtained from the dibromobenzene freezing at -7° . A third isomer, with a melting point of 106° , is converted into the same dibromobenzene with an f.p. of -7° , by reduction and replacement of the amino-group by hydrogen. Hence there are three isomeric nitrodibromobenzenes related to the dibromobenzene with f.p. -7° . This compound must therefore possess the *meta*-structure.

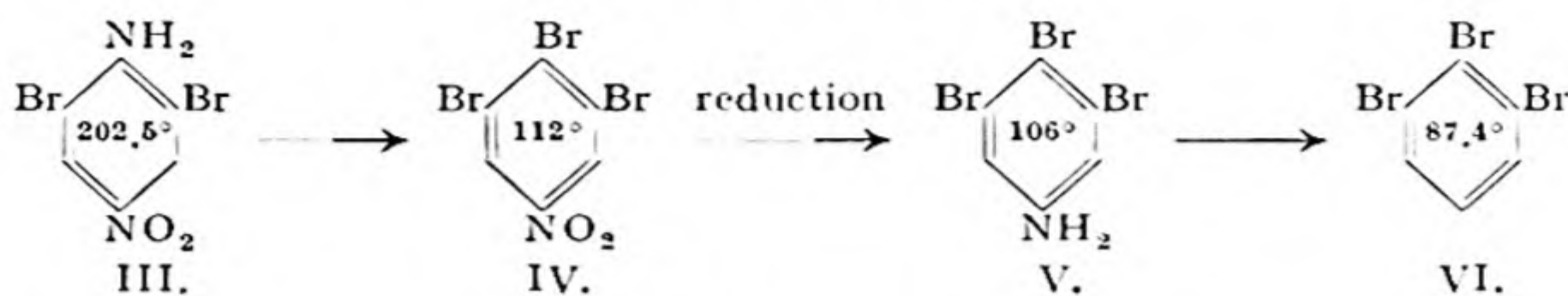
The dibromobenzene melting at 6° may have therefore either the *ortho*- or the *para*-configuration. If it is assumed that it is the *ortho*-compound, then the reactions described below can be represented as follows.

On nitration there is produced a dibromonitrobenzene melting at 58° , that is converted via an aminobromonitrobenzene into a dibromoaminonitrobenzene:



In compound III of the above reaction scheme, the two bromine atoms are situated in *meta*-positions, for, by replacing the amino-group by hydrogen, there is produced a dibromonitrobenzene, m.p. 64° , which is converted by reduction and replacement of the amino-group by hydrogen into *m*-dibromobenzene as shown above.

The amino-group in compound III can be replaced by bromine, the nitro-group can then be reduced to an amino-group which is subsequently replaced by hydrogen, to produce a tribromobenzene melting at 87.4° :



This tribromobenzene is not identical with the isomer melting at 44° , which is produced from the three isomeric dibromobenzenes and is therefore 1,3,4-tribromobenzene. It cannot be symmetrical tribromobenzene either, since this cannot be produced from *ortho*- or *para*-dibromobenzene, the starting materials in this particular case. Hence there remains only 1,2,3-tribromobenzene, but the starting material must have been *ortho*-dibromobenzene because 1,2,3-tribromobenzene cannot be produced from *para*-dibromobenzene if the bromine atoms originally present retain their positions. It is true that one of these bromines is replaced by NH_2 but this amino-group is again replaced by bromine. Hence there remains only the *para*-configuration for the third dibromobenzene melting at 89.3° . The structure of this compound is confirmed by the fact that only one nitrodibromobenzene can be derived from this compound.

GRIESS (1874) has employed the principal of KÖRNER for the absolute orientation of the three diaminobenzenes (phenylenediamines). In the nitration of *o*-nitrobenzoic acid he obtained three out of the four theoretically possible dinitrobenzoic acids. Two of these, melting at 179° and 202° , gave a diaminobenzene melting at 63° by reduction and removal of carbon dioxide. This compound could also be obtained from a dinitrobenzoic acid produced by nitrating *m*-nitrobenzoic acid. Since this diamino-compound may be obtained from three different dinitrobenzoic acids it must have the *meta*-structure.

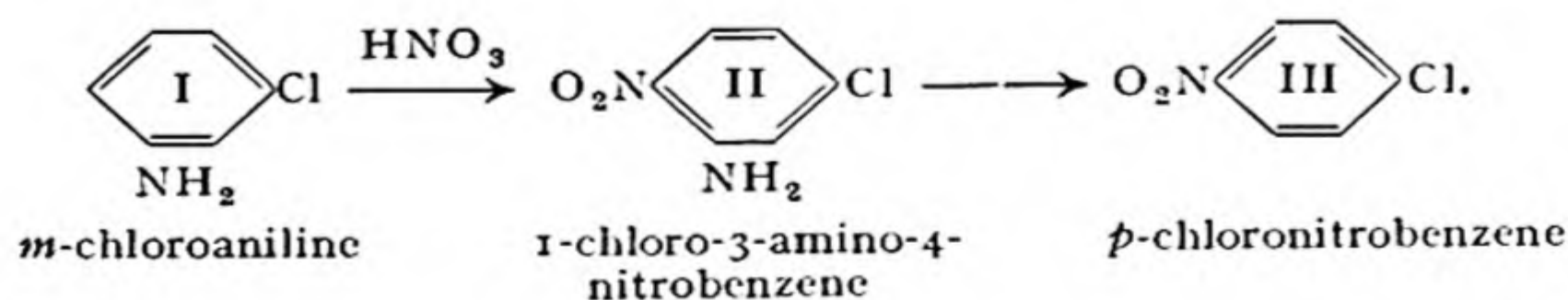
The third dinitrobenzoic acid, obtained from *o*-nitrobenzoic acid, is converted by reduction and fission of carbon dioxide into a phenylenediamine melting at 140° . This compound could be obtained from only one dinitrobenzoic acid so that the *para*-structure must be assigned to this diamine.

In another way, GRIESS prepared two diaminobenzoic acids, which cannot be derived from the three dinitrobenzoic acids mentioned above, for, when carbon dioxide was split off, they both produced a diaminobenzene melting at 103° , which must therefore be the *ortho*-compound.

Since *o*-, *m*- and *p*-diaminobenzene are produced by reducing the corresponding dinitro-compounds, the structure of these dinitrobenzenes is also established.

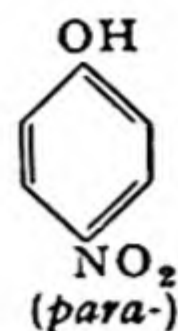
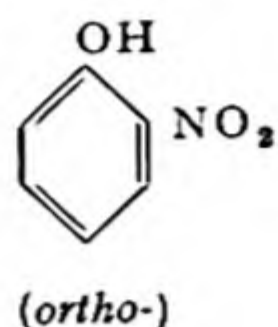
2nd. For tri-substitution products of benzene. These compounds can usually be orientated by investigating their relationship to disubstituted benzene derivatives of known structure.

By nitrating *m*-chloroaniline (I), a *nitrochloroaniline* (II) is produced. When the amino-group in this compound is replaced by hydrogen, *p*-chloronitrobenzene (III) is produced. This proves that the chloronitroaniline must have the structure (II) shown below:

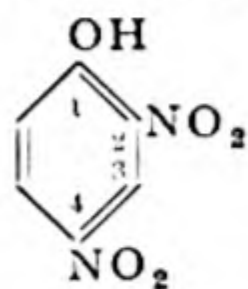


3rd. For tetrasubstituted derivatives of benzene, e.g. picric acid. By carefully nitrating

phenol, two mono-nitrophenols, melting at 45° and 114° , respectively, can be obtained:

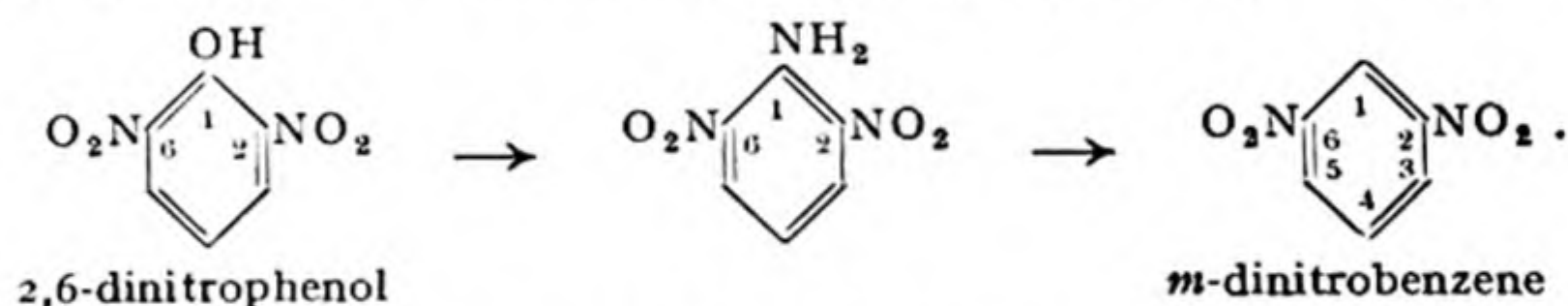


The third nitrophenol (m.p. 97°) is produced from *m*-dinitrobenzene (222) by reducing it to *m*-nitraniline and replacing the amino-group in the latter by hydroxyl by diazotisation. Hence the *ortho*- and *para*-configurations must be ascribed to the two isomers mentioned above.

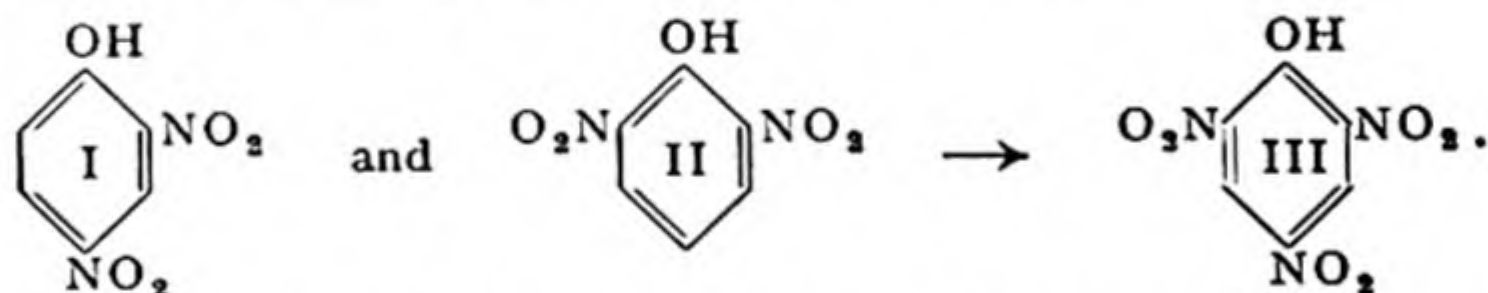


The mono-nitrophenol melting at 114° is converted into quinone on oxidation. Hence in this nitrophenol the hydroxyl and nitro-groups must be situated in the *para*-position to one another. Further, the *ortho*-structure only remains for the isomer melting at 45° .

o-Nitrophenol, m.p. 45° , on nitration gives two dinitrophenols, one of which has the 1,2,4-structure, because it is also produced by nitrating *p*-nitrophenol. The isomeric dinitrophenol has the 1,2,6-configuration, for, when the methyl ether is heated with alcoholic ammonia, the methoxyl group is replaced by NH_2 and the resultant amine gives *m*-dinitrobenzene when the amino-group is replaced by hydrogen:



Thus there are now two dinitrophenols of known structure:



Picric acid, which must therefore have structure III, is produced by nitrating either of the two isomeric dinitrophenols.

The structure of the trinitrobenzene melting at 123° follows from that of picric acid, which is produced from it by oxidation. Thus this trinitrobenzene must be the symmetrical isomer. It is produced by nitrating *m*-dinitrobenzene.

Rules for substitution in the benzene nucleus

272. Experience has shown, that on introducing a second substituent into a monosubstituted benzene derivative $\text{C}_6\text{H}_5\text{X}$, the three isomers theoretically possible are produced in unequal amounts and further, that two types of substitution may be distinguished, viz. either *ortho*- and *para*-compounds are formed as the chief reaction products or mainly *meta*-derivatives (*meta*-substitution) are produced as already mentioned by KÖRNER.

In Table 49 the main products are printed in heavy type and by-products are given in order of decreasing amounts produced.

TABLE 49
SUBSTITUTION IN THE BENZENE NUCLEUS

Element or group already occupying position 1.	Positions entered by the substituents given below:				
	Cl	Br	I	SO ₃ H	NO ₂
Cl	4, 2, 3	4, 2, 3	4	4	4, 2
Br	4, 2, 3	4, 3	—	4	4, 2
I	4	4	4	4	4, 2
OH	4, 2	4, 2	4, 2	4, 2	4, 2
SO ₃ H	—	3	—	3, 4	3, 2, 4
NO ₂	3	3	—	3, 2, 4	3, 2, 4
NH ₂	4, 2	4	4	4, 2	4, 2
CH ₃	4, 2, 3	4, 2	4, 2,	4, 2, 3	2, 4, 3
COOH	3	3	3	3, 4	3, 2, 4
CN	3	3	—	—	3
NO	4	4	—	—	4
SCH ₃	—	4, 2	—	4, 2	—

From the table, it appears that the halogens, the hydroxyl, the methyl, the nitroso- and the methylmercapto-groups direct a second substituent to the *ortho-para*-positions, while the sulpho-, the nitro-, the carboxyl and the cyano-groups direct the second substituent mainly towards the *meta*-position no matter what the nature of the second substituent.

This is known as *the rule of the constancy of the substitution type* (CRUMBROWN-GIBSON; HOLLEMAN).

HOLLEMAN and his pupils have carried out systematic investigations on the relative amounts of the various isomers produced by the introduction of a substituent into a mono- or di-substituted benzene derivative. For this purpose it was necessary to work out methods for determining the ratio of the isomers in the reaction product, because quantitative separation is not usually possible, on account of the small differences in solubility or boiling point of the isomeric compounds.

These methods depend on the following principle. In the case of a mixture of two isomers the melting point curve of the two compounds is determined; by determining the melting point (or setting point) of the various mixtures it is possible to find the composition of every possible mixture of these isomers.

This method of *thermal analysis* has also been worked out for mixtures of three isomers and in special cases it can also be applied to a mixture of four isomers.

From these investigations it was found that the relative quantities in which the isomers are produced, differ very considerably, even in the same type of substitution and are dependent on the nature of the substituents

already present, on the entering substituent and on the temperature. Thus in the chlorination of phenol at 90° there is produced 50.2 % of *p*-chlorophenol and 49.8 % of *o*-chlorophenol; in bromination under the same conditions there is produced 90.7 % of *p*- and 9.3 % of *o*-bromophenol.

The effect of temperature in nitration is small. These reactions can only be investigated within a small range of temperatures, since at high temperature the action of nitric acid is too violent and decomposition occurs. The influence of temperature is of more importance in sulphonation. A very striking influence of temperature has been observed, however, in halogenation (WIBAUT with VAN DE LANDE and WALLAGH and with VAN LOON).

On brominating bromobenzene in the vapour phase with pumice or graphite as contact substance at 400° , there is produced a mixture of dibromobenzenes containing 26 % *ortho*-, 33 % *meta*- and 40 % *para*-isomer; thus the reaction belongs to the *ortho-para*-substitution type.

At 450° , 21 % *ortho*-, 50 % *meta*- and 25 % *para*-dibromobenzene is formed; in this case *meta*-substitution predominates. The ratio of isomers does not alter appreciably at higher temperatures up to 630° . It is assumed that above 450° the bromine atom in bromobenzene no longer has a directing influence. Since the five available atoms of hydrogen have an equal chance of being substituted by bromine, there should be produced 40 % *ortho*-, 40 % *meta*- and 20 % *para*-bromobenzene. Substitution in the *ortho*-positions is hindered, however, by the effect in space of the bromine atom attached to the benzene nucleus (*steric hindrance*; compare 273). Therefore less than 40 % of the *ortho*-isomer will be produced. Independent of the *ortho*-content, the ratio of *meta*:-*para*- must be 2 : 1, which agrees approximately with the observed values. If pumice covered with ferric bromide is used as catalyst the reaction takes place at a measurable rate even at 200° . In this case the *ortho-para*-substitution type persists to 450° . At this temperature 28 % *ortho*-, 14 % *meta*- and 58 % *para*-isomer is formed. The reaction occurs in the surface layer of ferric bromide according to the electrophilic type of substitution (see 224). As the temperature rises, adsorption of the reacting substances at the solid surface decreases, so that a true gas-reaction comes to the fore in place of the wall-reaction. This gas-reaction probably takes place by another mechanism. Since the reacting substances will be more strongly adsorbed on ferric bromide than on pumice, it is understandable that *ortho-para*-substitution will still occur on a ferric bromide catalyst at 450° . Similar phenomena are observed in the bromination of fluoro- and chloro-benzene. *Meta*-substitution also takes place as the main reaction in the chlorination of chlorobenzene in the vapour phase at 500 – 600° with pumice as contact material.

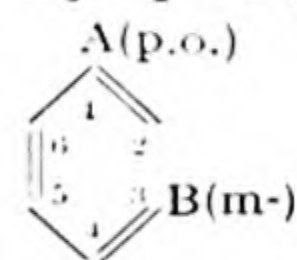
In the presence of pure pumice as contact material, the bromination of phenol in the vapour phase takes place very rapidly. In this case *para-ortho*-substitution occurs exclusively in the region of 200 – 250° ; the proportion of *ortho*-bromophenol increases with the temperature and amounts to 70 % in the mixture of mono-bromophenols formed at 500° . It is assumed that the bromination of phenol takes place by a different mechanism from the bromination of halogenobenzenes.

The following question may be asked in connection with the introduction

of a third substituent C into a benzene derivative C_6H_4AB . If it is known which isomers and in what ratio they are formed in the substitution of C into C_6H_5A and C_6H_5B , is it possible to deduce which isomers of the composition C_6H_3ABC and in what ratio they will be produced, in the substitution of C in C_6H_4AB ? This can be done qualitatively.

The velocity with which a new substituent enters a benzene derivative, varies considerably. Substitution in the *meta*-positions under the influence of the nitro-, carboxyl, sulpho- and cyano-groups takes place much more slowly than substitution under the influence of *ortho*- and *para*-directing-groups. The nitration of benzene, toluene or chlorobenzene with a mixture of sulphuric and nitric acids takes place much too rapidly for the reaction velocity to be measured; it has been possible to carry out such measurements in the nitration of nitrobenzene and benzoic acid, since the reaction takes place much more slowly in these cases.

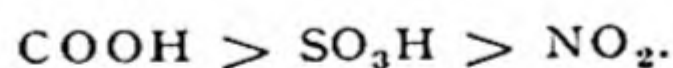
When a third substituent is introduced into a benzene derivative C_6H_4AB , in which A directs towards *ortho*- and *para*-positions and B towards *meta*, experiment shows that the third substituent enters positions 2, 4 or 6 (or in all three) but never in position 5. From this it follows that *ortho-para*-substitution takes place much more rapidly than *meta*-substitution. In the introduction of a third group into a compound C_6H_4AB , in which both A and B direct towards *ortho*- and *para*-positions, it appears, that the directing effect of one of these substituents may predominate. Thus in *o*-cresol, $C_6H_4(OH)CH_3$ -1,2, for example, a third substituent enters positions 4 and 6 (*i.e.* *ortho-para* with respect to OH) and not positions 3 and 5 standing in *ortho*- and *para*-position to CH_3 .



By studying substitution in other compounds of the type C_6H_4AB , in which A and B are *ortho*-substituents, in a similar way, the following order is arrived at for the directive influence of two substituents present at the same time (HOLLEMAN):



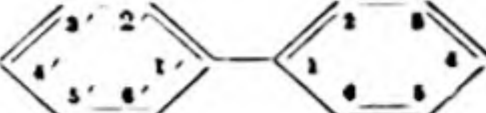
In a similar way *meta*-directing groups arrange themselves in the following order:



From the above, it is possible also to predict which isomers will be formed in any particular case and which isomer is likely to be the main product. For example, when a substituent is introduced into a chlorophenol, it will enter mainly the *ortho*- and *para*-positions with respect to the hydroxyl group; in a chlorobenzoic acid, a third substituent will enter the *ortho*- and *para*-positions to the chlorine.

(xvi) HYDROCARBONS WITH TWO OR MORE PHENYL GROUPS

273. The simplest compound belonging to this group is *diphenyl*

, which occurs in coal-tar.

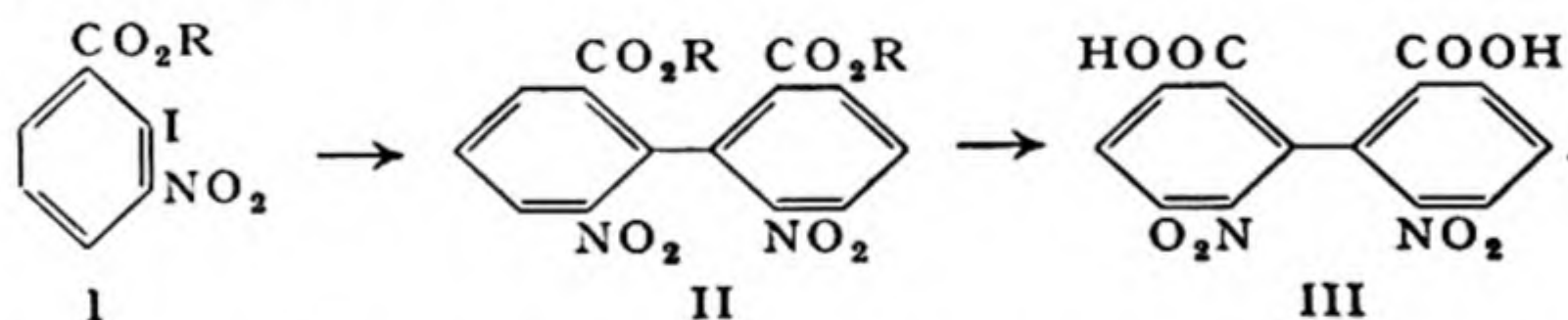
It can be obtained by heating iodobenzene with finely divided copper to 220° or by passing benzene vapour through a tube heated to $700-800^{\circ}$ (BERTHELOT); it is prepared on a commercial scale by the latter process.

Diphenyl melts at 71° and boils at 254° . It is readily nitrated and sulphonated. It affords benzoic acid on oxidation; this fact and its mode of formation establish its structure.

The number of substitution products of diphenyl is much greater than that of benzene. Mono-substitution products can exist in three isomeric forms, viz. *o*-, *m*- and *p*- with respect to the I—I' bond. In a di-substituted product both substituents may be present in the same or in different benzene nuclei.

Some derivatives of diphenyl, *e.g.* benzidine (243), are of importance as dyestuffs intermediates.

Some remarkable cases of stereoisomerism have been discovered amongst substitution products of diphenyl. By the action of copper powder on an ester of 2-iodo-3-nitrobenzoic acid (I), a diphenyl derivative is produced (II), which is converted into dinitrodiphenic acid (III) on hydrolysis:

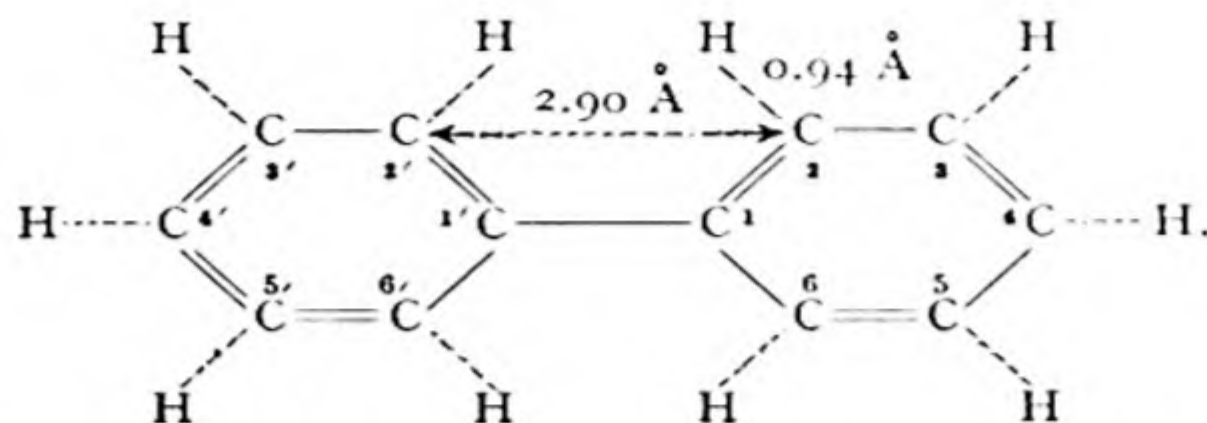


This acid can be resolved into optical antipodes via the brucine salt (KENNER and CHRISTIE). This must be explained by the fact that the two benzene rings in this diphenyl derivative do not lie in the same plane. Two space-figures can then be constructed, which are mirror images of one another, as appears from the figures given below, in which one benzene ring is represented as lying in a plane perpendicular to that of the other ring. Although there is no asymmetric carbon atom in this molecule, the latter contains neither a centre nor a plane of symmetry (37):



The two mirror image forms should be interconvertible if the two substituted phenyl groups were able to rotate about the axis of the common C—C bond. This is apparently hindered by the presence of the groups substituted in the *ortho*-positions with respect to the common bond and which cannot rotate past each other because of the volume

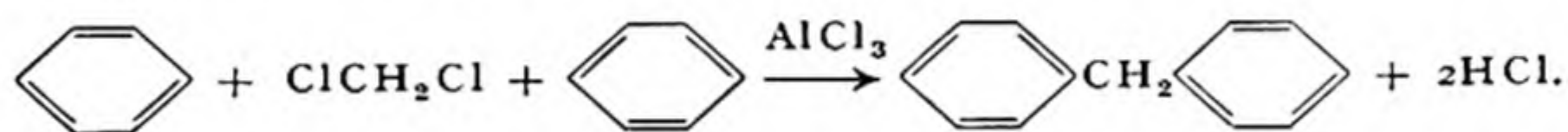
in space they occupy (*steric hindrance*). In diphenyl itself the two benzene nuclei can rotate with respect to one another because the distance between the nuclei of carbon atoms 2 and 2' is about 2.90 Å and the length of the C—H bond 0.94 Å (see 37):



When positions 2–2' and 6–6' are occupied respectively by COOH and NO₂ these groups cannot pass one another because the distance C—NO₂ is about 1.92 Å and the distance C—COOH about 1.56 Å; rotation of the phenyl groups about the 1–1' bond is hindered (ADAMS).

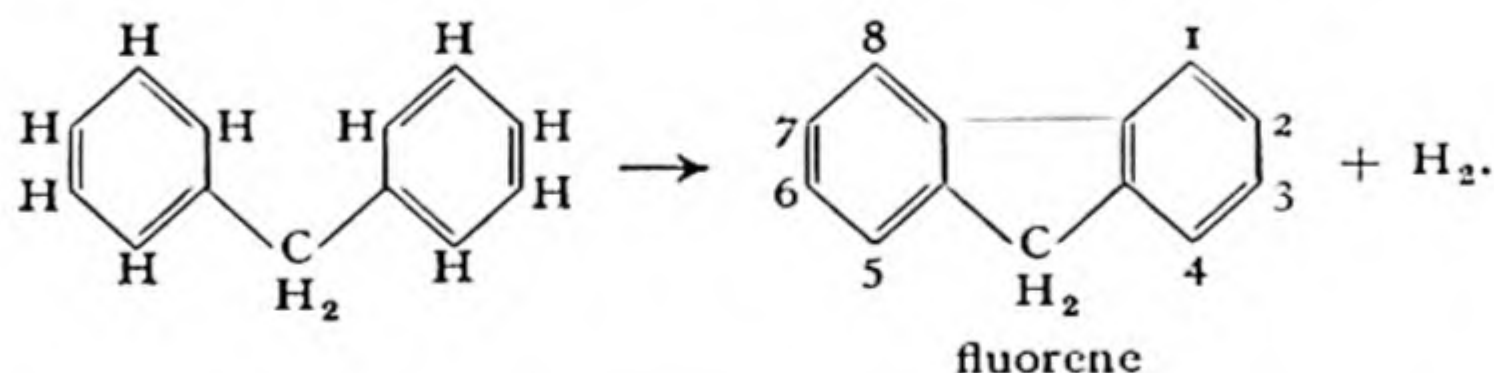
A large number of diphenyl derivatives, which can be resolved into optically active components, has been prepared. Many of these compounds are converted into an optically inactive mixture (racemisation) by warming, the change taking place the more readily as the groups substituted in positions 2–2' and 6–6' take up a smaller volume. Hence on increasing the temperature, the ability to rotate about the common C—C bond can reach an appreciable value.

Diphenylmethane C₆H₅CH₂C₆H₅, can be obtained from benzyl chloride, C₆H₅CH₂Cl, or from methylene chloride CH₂Cl₂, benzene and aluminium chloride:

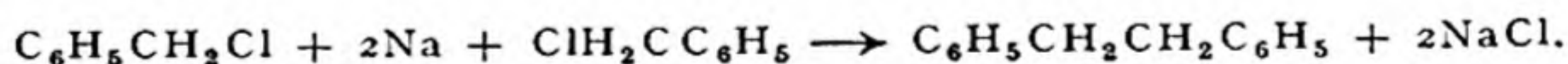


Diphenylmethane melts at 26° and boils at 262°, and has an odour of orange skins. It is converted into benzophenone (259) by oxidation with chromic acid.

When diphenylmethane is passed through a tube heated to about 700°, hydrogen is produced along with *fluorene*, a stable hydrocarbon, melting at 115° and boiling at 249°, which shows a weak fluorescence in alcoholic solution:



Diphenylethane or *dibenzyl* C₆H₅CH₂CH₂C₆H₅, m.p. 52°, can be obtained from phenylchloromethane (benzyl chloride) and sodium:

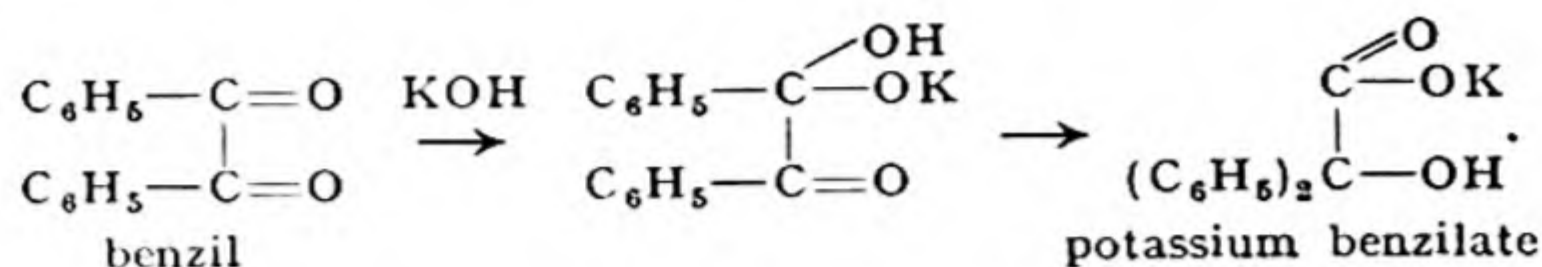


Benzoin, mentioned in 257, is a derivative of diphenylethane. On reduction, this compound takes up two atoms of hydrogen with the formation of the di-hydric alcohol, *hydrobenzoin* or 1,2-diphenylethanediol-1,2 C₆H₅CHOHCHOHC₆H₅.

On oxidising benzoin, a diketone is produced, namely, *dibenzoyl* or *benzil*, C₆H₅CO—COC₆H₅, a yellow, crystalline substance melting at 95°.

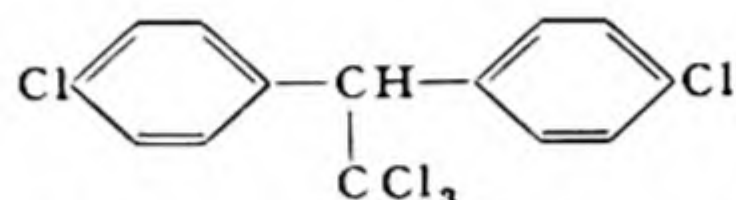
On heating with alcoholic potash, benzil takes up a molecule of KOH and undergoes

an intramolecular transformation with the formation of the potassium salt of benzoic acid:



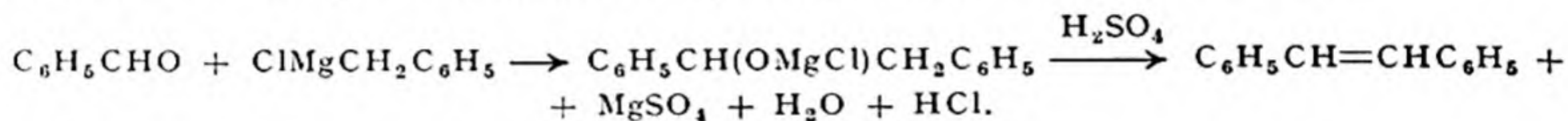
This transformation is analogous to the pinacolone transformation (110).

2,2-bis(4'-Chlorophenyl)-1,1,1-trichloroethane is obtained by the condensation of chloral with two molecules of chlorobenzene. It has powerful insecticidal properties and acts as a contact poison. It is known under the names of Gesarol, Neocid and D.D.T. It is used for destroying lice, moths, flies, etc.:

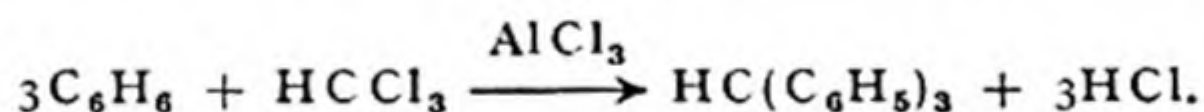


2,2-bis(4'-chlorophenyl)-1,1,1-trichloroethane or D.D.T.

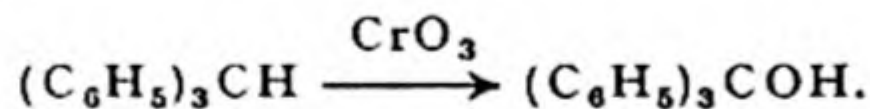
Diphenylethene or stilbene, $\text{C}_6\text{H}_5\text{CH}=\text{CHC}_6\text{H}_5$ (m.p. 125° , b.p. 307°) can be prepared, for example, by the action of benzylmagnesium chloride on benzaldehyde and distillation of the product obtained by acidification with sulphuric acid:



Triphenylmethane $(\text{C}_6\text{H}_5)_3\text{CH}$ is produced by the action of benzene on benzaldehyde in presence of a dehydrating agent like zinc chloride, or by reacting benzene with phenyldichloromethane (benzal chloride) $\text{C}_6\text{H}_5\text{CHCl}_2$ or with chloroform in the presence of aluminium chloride:



Triphenylmethane melts at 93° and boils at 359° . It is oxidised by chromic acid to triphenylcarbinol:



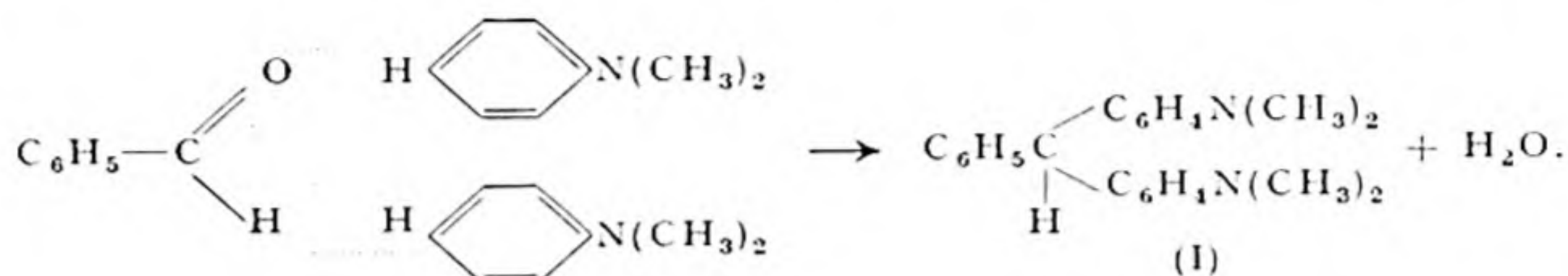
Under the influence of the three phenyl groups, the CH-group has attained an enhanced reactivity (compare the oxidation of diphenylmethane to benzophenone, p. 441).

Dyestuffs derived from Triphenylmethane

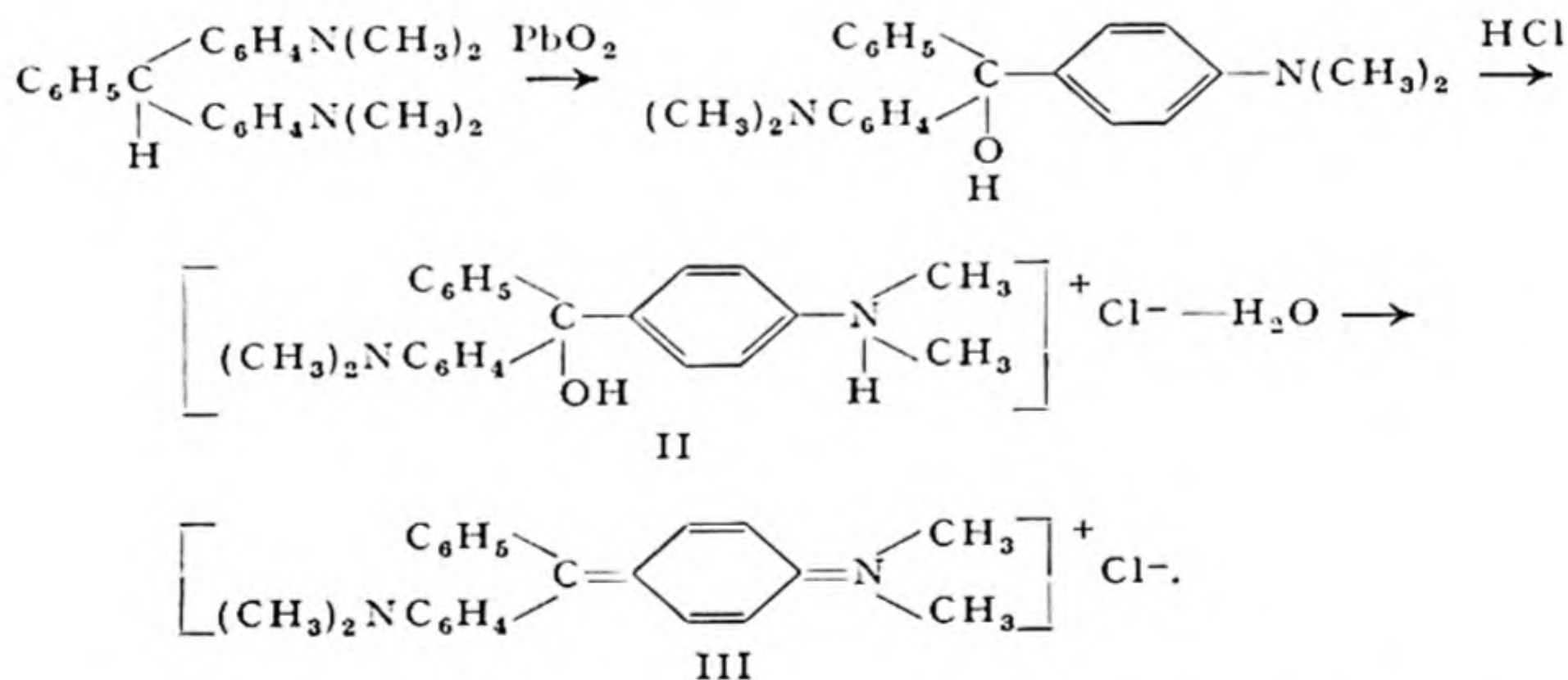
274. Rosaniline dyestuffs. These were discovered in 1859 by VERGUIN; the first synthetic dyestuff had been discovered in 1856 by W. H. PERKIN and the synthetic dyestuffs industry can be said to date from that time. The structure of the rosaniline dyestuffs was established by researches carried

out by E. and O. FISCHER, HOFMANN, NIETSKI, BAEYER, W. H. PERKIN and others.

Malachite Green is obtained by condensing benzaldehyde with dimethylaniline (237) in the presence of zinc chloride (cf. the preparation of triphenylmethane by a similar method), the carbon atom of the aldehyde grouping providing the carbon atom of the methane residue in the triphenylmethane derivative. The colourless intermediate product, which is produced in this case, is *tetramethyldiaminotriphenylmethane* or leuco-malachite green (I):



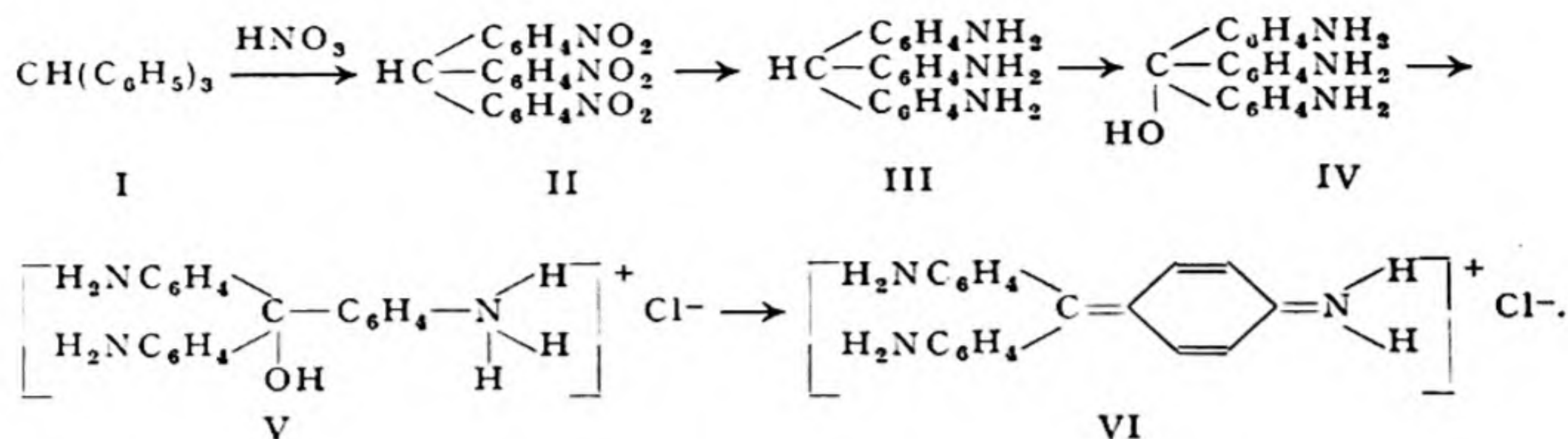
By oxidation with lead peroxide in hydrochloric acid solution, I is converted into the chloride of Malachite Green (III). The reaction probably takes place via the colourless *methanol derivative* or *carbinol base*, which can give colourless salts with acids (II) like the amine base, but such salts are difficult to isolate:



On warming, II loses water and is converted into the intense green dyestuff having structure III. In this conversion, one of the benzene nuclei assumes a quinonoid structure. The double salt of compound III with zinc chloride is Malachite Green.

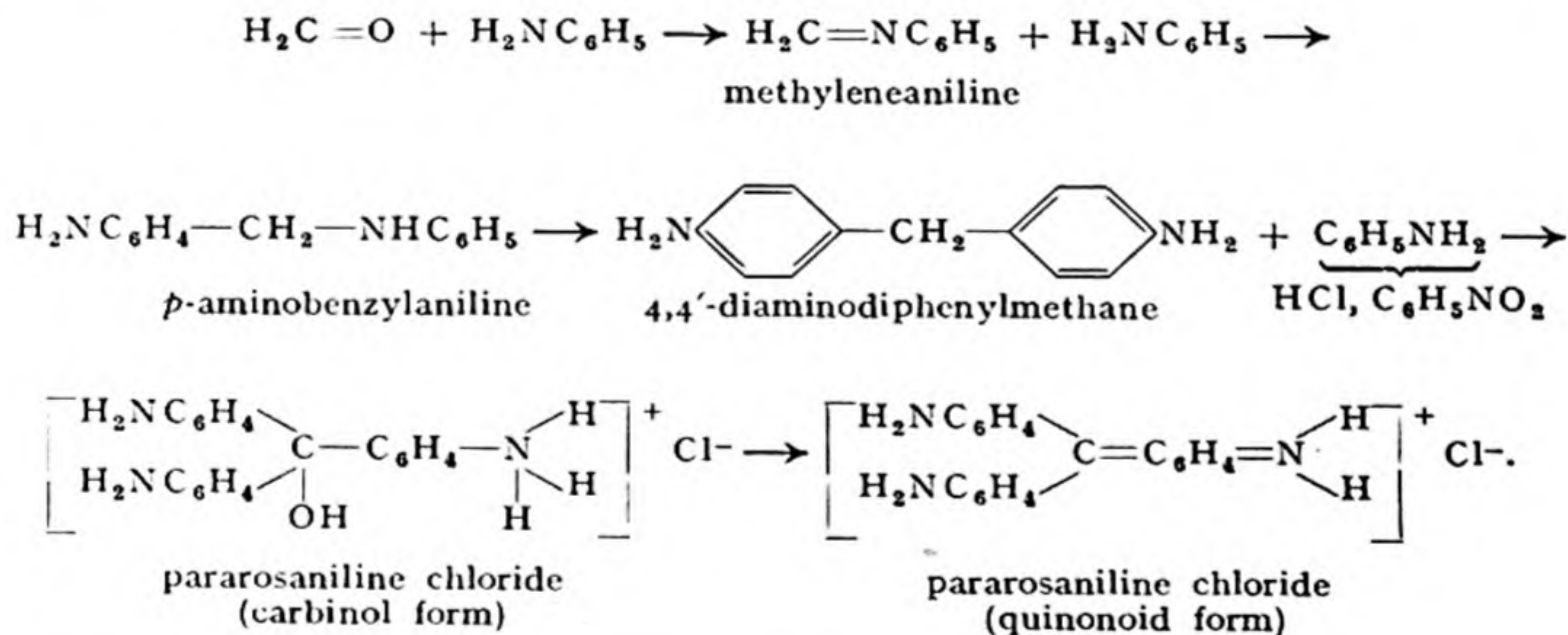
Pararosaniline. The structure of this red dyestuff follows from the synthesis by E. and O. FISCHER (1880). By nitrating triphenylmethane (I), a trinitro-derivative (II) is produced, which can be reduced to a triamino-compound, the so-called *leucaniline*, (III), a colourless substance, melting at 148°. This compound on oxidation gives a colourless carbinol base (IV), *pararosaniline base*, which on warming in hydrochloric acid, forms first the

salt (V) and then the dyestuff hydrochloride, *pararosaniline chloride* (sometimes called *parafuchsine*) (VI).:

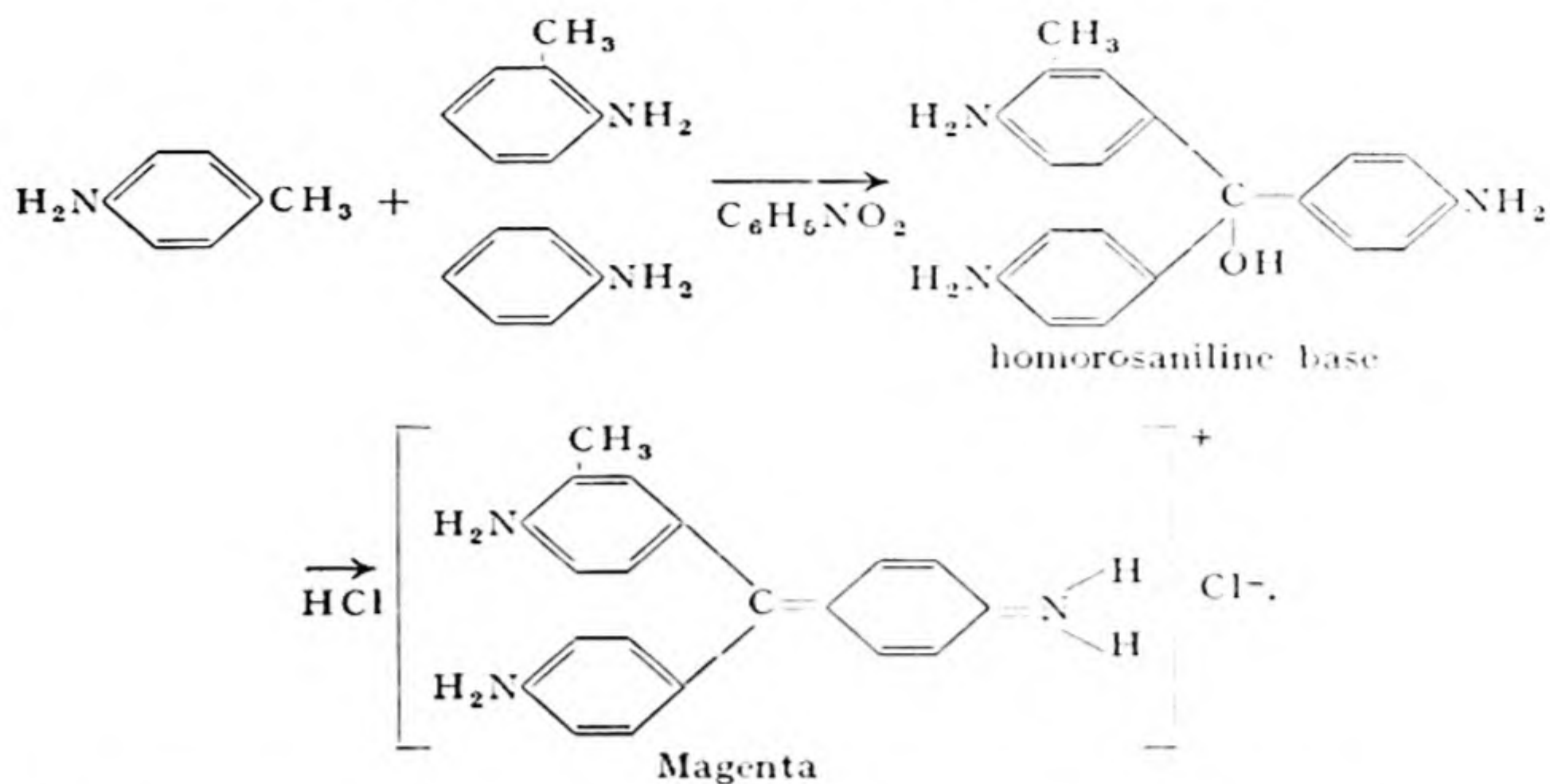


Conversely, *paraleucaniline* (III) can be obtained by reducing *pararosaniline* hydrochloride (VI) and the amino-groups can be replaced by hydrogen by deamination, with the formation of triphenylmethane (I).

A technical method for the preparation of *pararosaniline* starts from aniline and formaldehyde (HOMOLKA), which interact to form *methyleneaniline*, which is converted in its turn, via *p*-aminobenzylaniline, into *4,4'*-diaminodiphenylmethane by heating with aniline and aniline hydrochloride. By heating further with aniline, hydrochloric acid and nitrobenzene (as an oxidising agent) *pararosaniline chloride* is formed:



Magenta (Fuchsine), another red dyestuff of great importance, is essentially *homorosaniline*, a methyl derivative of *pararosaniline*, usually containing some of the latter dyestuff. It is prepared on a technical scale by oxidising a mixture of equal parts of aniline, *o*-toluidine and *p*-toluidine with nitrobenzene or arsenic acid to form the *rosaniline* base, which is converted into *magenta* with hydrochloric acid. The carbon atom of the methane residue is provided by the *p*-toluidine (*pararosaniline* can be prepared by an analogous process using 2 mols. of aniline and 1 mol. of *p*-toluidine):

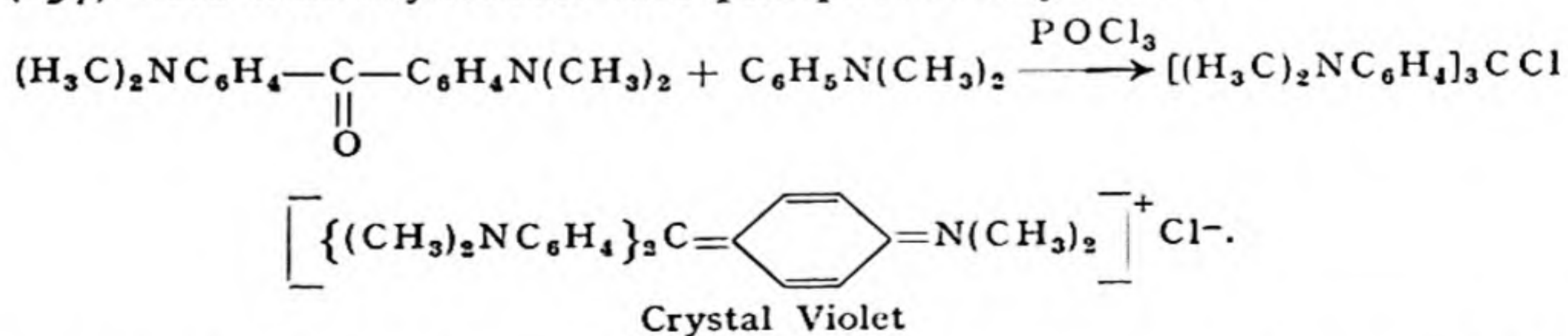


Many derivatives of magenta and pararosaniline are used as dyestuffs; the hydrogen atoms in the amino-groups can be replaced by alkyl or phenyl residues, when the colour is displaced progressively towards violet as the number of methyl groups attached to nitrogen is increased; in pararosaniline, for example, the absorption maximum lies at 5000 Å, while in Crystal Violet in which there are six methyl groups attached to nitrogen, this maximum lies at 6000 Å.

Magenta and related dyestuffs in the crystalline state show powerful reflecting power for light of those wave-lengths which are strongly absorbed by transmitted light (metallic reflection). Consequently, in incident light, these crystals appear to have a colour (*colour of reflection*) which is approximately the complementary colour to that observed in transmitted light. Pararosaniline and magenta, for example, crystallise in green, crystalline leaflets with a brilliant metallic sheen, which dissolved in water giving an intense red solution.

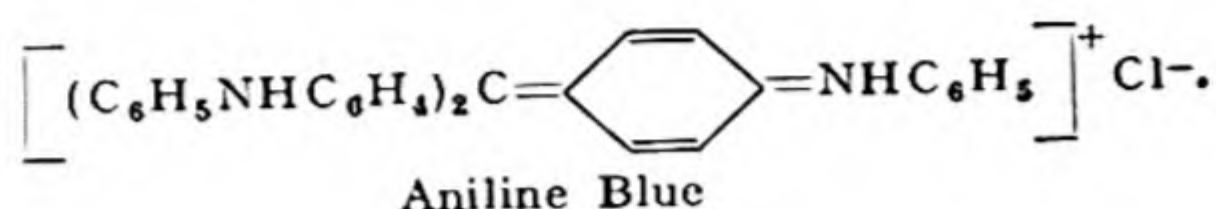
The various brands of *Methyl Violet* are alkylated pararosanilines. The red shade brands (R, 2R, 3R) are made by methylating pararosaniline but the bluer shade brands (B, 2B, 4B, 6B) are made by other methods. Thus *pentamethylpararosaniline* is produced by oxidising dimethylaniline with potassium chlorate and cupric chloride; in this process one of the methyl groups is eliminated by oxidation as formaldehyde, which then provides the central carbon atom of the triphenylmethane group. Methyl Violet is used in the preparation of copying ink etc.

Crystal Violet or hexamethylpararosaniline, is produced by heating MICHLER's ketone (237) with dimethylaniline and phosphorus oxychloride:



Aniline Blue (Spirit Blue) or *triphenylrosaniline*, a pure blue dyestuff, is obtained by heating together pararosaniline, aniline and a weak acid, e.g. benzoic acid; the

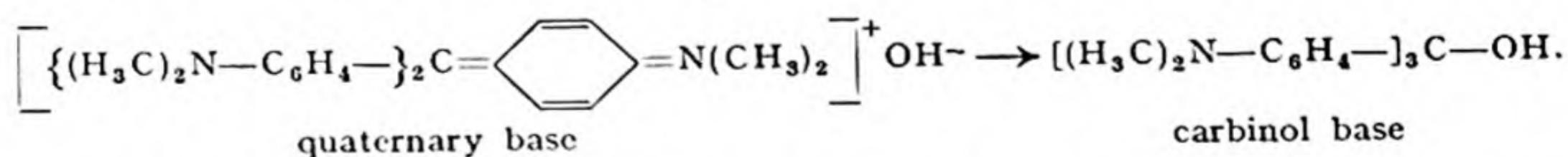
amino-groups are replaced by phenylamino-groups and the liberated ammonia is fixed by the benzoic acid. This reaction is similar to the formation of diphenylamine from aniline and aniline hydrochloride (237):



Rosaniline dyestuffs can be used for dyeing wool and silk directly and cotton after treatment with a mordant (*e.g.* tannic acid).

275. *The relationship between colour and structure in rosaniline dyes*

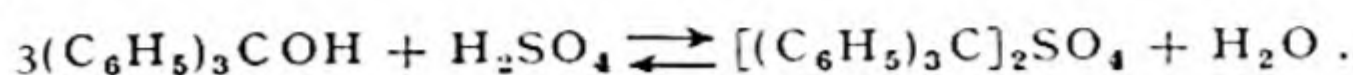
It has already been explained that the actual dyestuffs are salts; these dyestuff salts are almost completely dissociated in dilute aqueous solution as appears from the small increase in the molecular conductivity on further dilution. Solutions of salts of magenta with different anions (chloride, bromide, sulphate) show the same absorption spectrum. From these observations it follows, that the colour of magenta is caused by the mono-valent cation $(\text{C}_{20}\text{H}_{20}\text{N}_3)^+$; a similar conclusion is reached for other rosaniline dyestuffs. In the structural formulae for Malachite Green, Magenta and Pararosaniline (pp. 444) it is assumed that one quinonoid group occurs in the cation; this mode of formulation which was suggested by NIETZKI in 1890, was strengthened by HANTZSCH (1900) as follows. When an equivalent of base is added to a solution of a dyestuff salt, *e.g.* of Crystal Violet, initially the solution remains coloured and reacts strongly alkaline. Gradually, the colour, the basicity and the electrical conductivity of the solution all decrease. In the original solution, a very strong base, therefore a quaternary ammonium base, must have been present; this can only occur if one of the nitrogen atoms is attached to a carbon atom of a quinonoid group by two homopolar bonds. This quaternary base, which gives rise to a coloured cation, gradually passes over into a colourless, weakly basic carbinol base:



The carbinol base may be regarded as a *pseudo-base* (cf. pseudo-acids 226). The dyestuff cations contain the chromophoric quinonoid group and the auxochromic amino- or dialkylamino-groups.

Triphenylmethane derivatives are known in which the colour is not caused by a quinonoid structure (BAEYER and VILLIGER, GOMBERG, HANTZSCH). *Triphenylchloromethane* $(\text{C}_6\text{H}_5)_3\text{CCl}$, which can be obtained from carbon tetrachloride and benzene by allowing them to react in the presence of aluminium chloride, is colourless in the solid state or when dissolved in ether or benzene. In liquid sulphur dioxide, however, it dissolves with a yellow colour; this solution conducts electricity, while the solution in

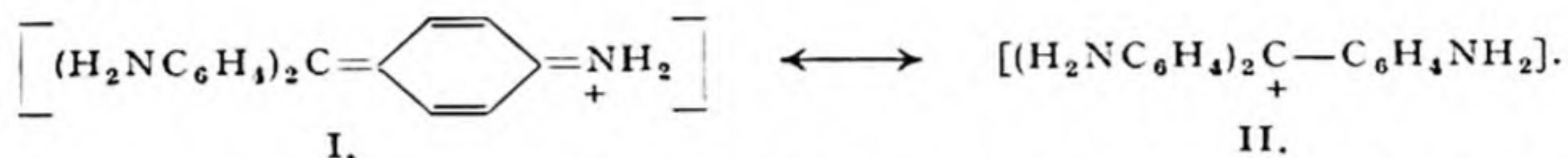
ether or benzene is non-conducting. This compound, which is known also as *triphenylmethyl chloride* is produced also by the action of hydrochloric acid on *triphenylcarbinol*; the hydroxyl group in this tertiary alcohol can be replaced also by other inorganic acid residues thus:



Triphenylmethyl sulphate dissolves with a red colour in liquid sulphur dioxide and the solution conducts an electric current; triphenylmethyl perchlorate is also coloured. These compounds are regarded as *carbonium salts* in which the cation $[(\text{C}_6\text{H}_5)_3\text{C}]^+$ occurs; this cation contains no quinonoid grouping, the colour of the salts is connected apparently with the positively charged *carbonium ion*. BAEYER named this phenomenon *halochromism* to express that the colour is connected with a salt-like structure.

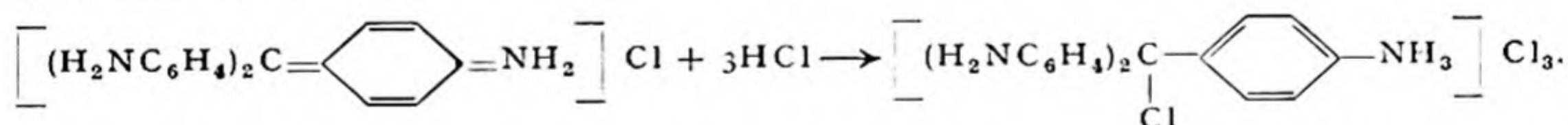
Triphenylcarbinol is a very weak base, since the carbonium salts easily undergo hydrolytic fission unlike the dyestuff salts such as Magenta etc., which are derived from a strong quaternary ammonium base and which are not decomposed by boiling an aqueous solution.

According to more recent ideas, the colour of the rosaniline dyestuffs is not due entirely to cations with a quinonoid structure but it is assumed that the cations of these dyestuffs can resonate between the quinonoid structure (I) and the carbonium structure (II):

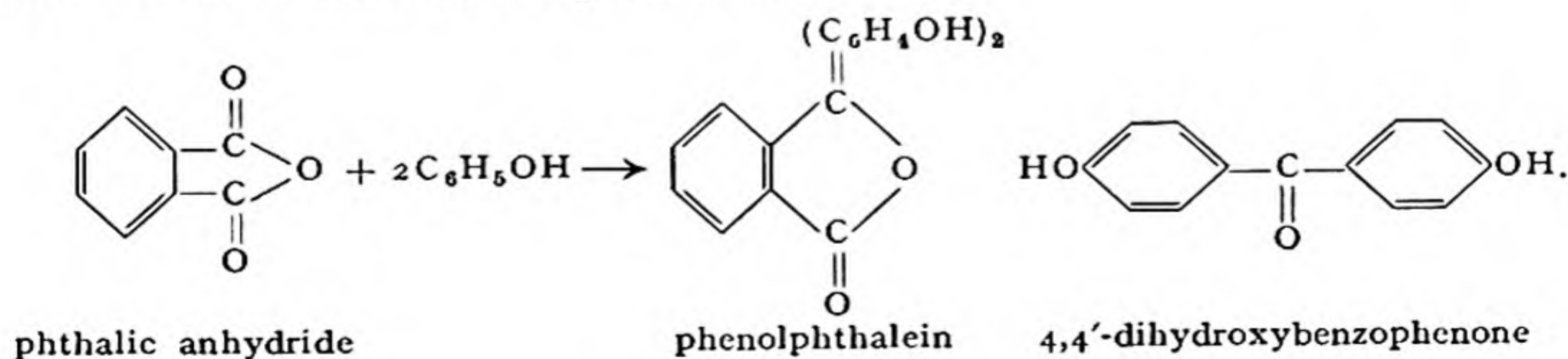


Various valence-structures are still possible for the cation I, since each of the three $-\text{C}_6\text{H}_4$ -groups can assume a quinonoid structure.

Pararosaniline chloride or Magenta dissolve in an excess of strong hydrochloric acid with a pale yellow colour; the red colour reappears when the solution is diluted with water. In the strongly acid solution it is probable that three molecules of hydrochloric acid combine with the dyestuff; in the resultant cation the formation of a quinonoid structure is no longer possible, so that the colour approaches that of the carbonium salts:

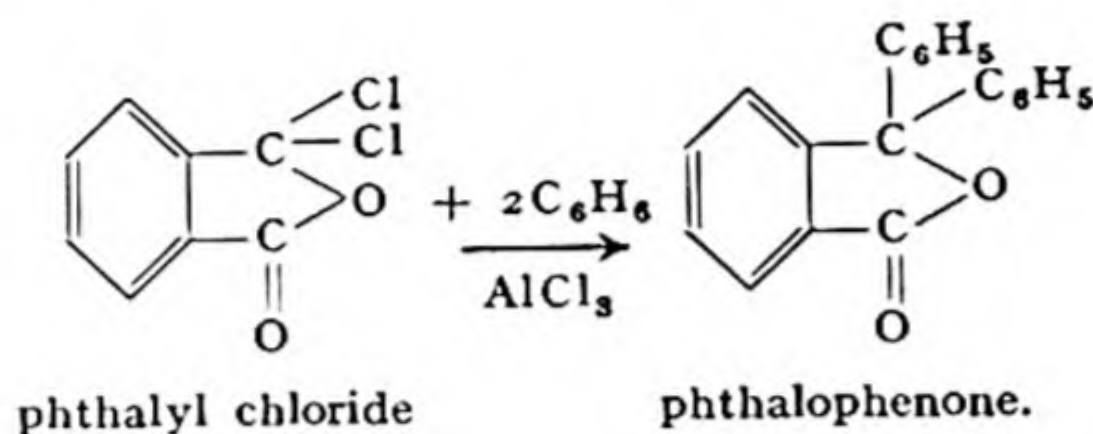


276. Phthalein dyestuffs. The simplest compound belonging to this group is *phenolphthalein*, a colourless, crystalline compound, which dissolves in alkaline liquids with the production of a red colour and is used as an indicator in alkalimetry. The colour change with phenolphthalein takes place at $\text{pH} = 8 - 10$. It is prepared by heating together phthalic anhydride and phenol in concentrated sulphuric acid:



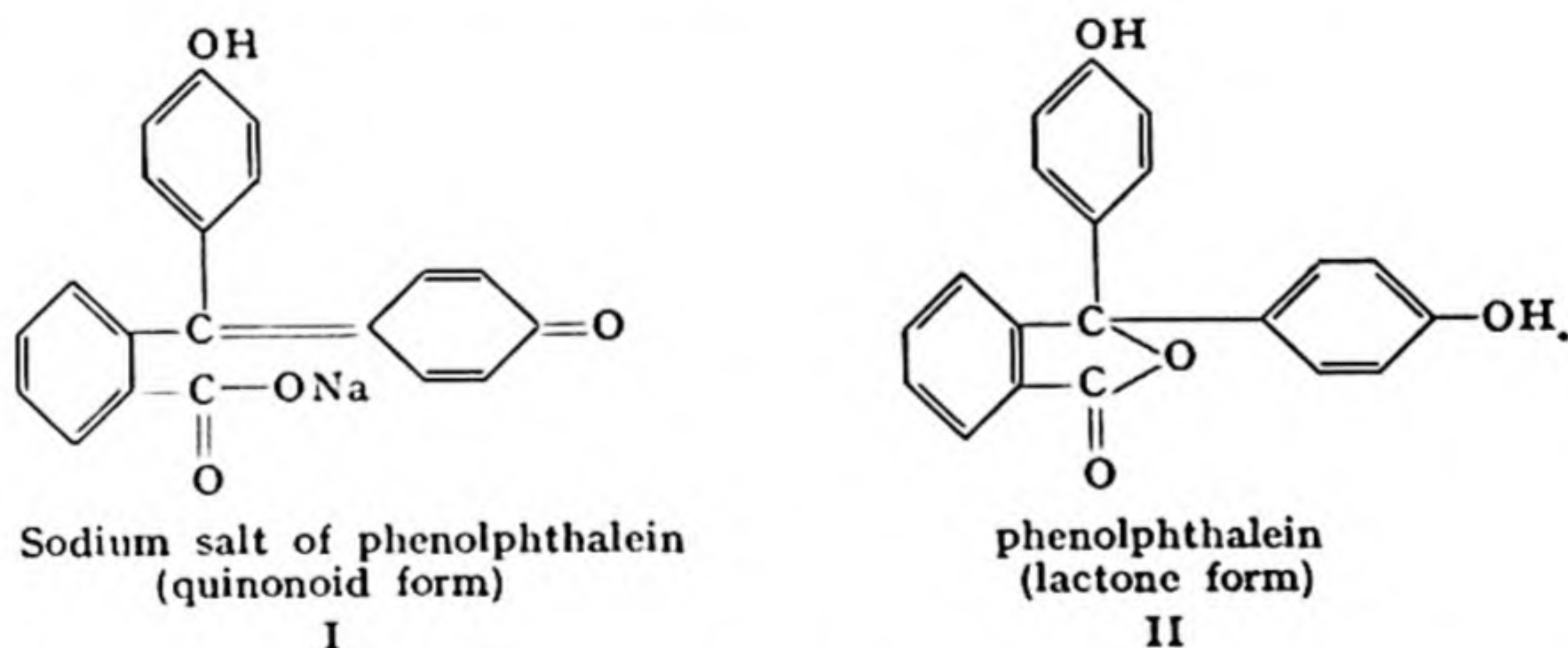
The hydrogen atoms occupying the *para*-positions to the hydroxyl groups in the phenol molecules react, as is shown by the fact that phenolphthalein is converted into *4,4'-dihydroxybenzophenone* when fused with potash.

The structure of phenolphthalein appears also from its relationship with *phthalophenone*. This substance can be obtained from phthalyl chloride (266) and benzene in the presence of aluminium chloride:



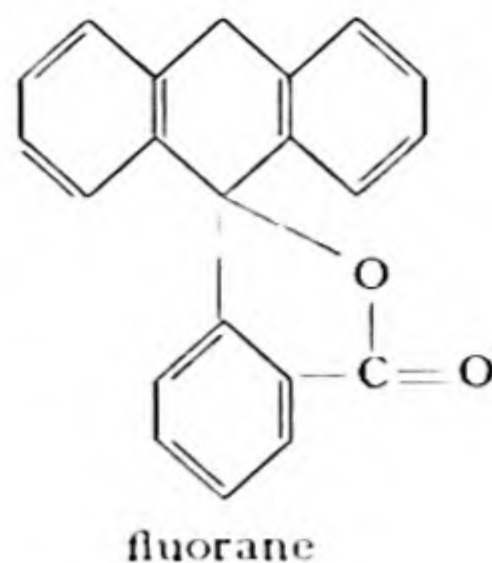
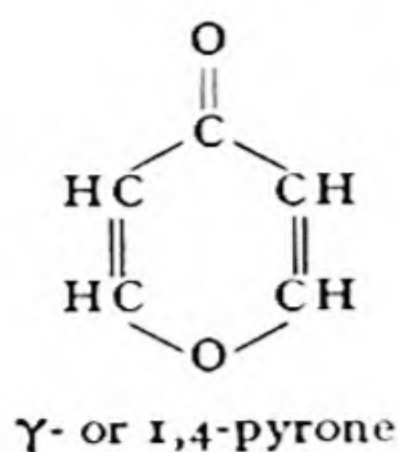
On reduction, phthalophenone is converted into triphenylmethane carboxylic acid $(\text{C}_6\text{H}_5)_2\text{CH}-\text{C}_6\text{H}_4-\text{COOH}$, which gives triphenylmethane on heating with barium hydroxide. This, along with its mode of formation, proves the structure of phthalophenone. By nitrating the latter, a dinitro-phthalophenone is produced, which can be converted, via the diamino-compound and replacement of the amino-groups by hydroxyl (by diazotisation), into phenolphthalein.

Colour change of phenolphthalein in alkaline solution. By the action of an equivalent quantity of sodium hydroxide on phenolphthalein, there is produced the mono-sodium salt, which is bright red in colour in solution and is assigned the following structure:



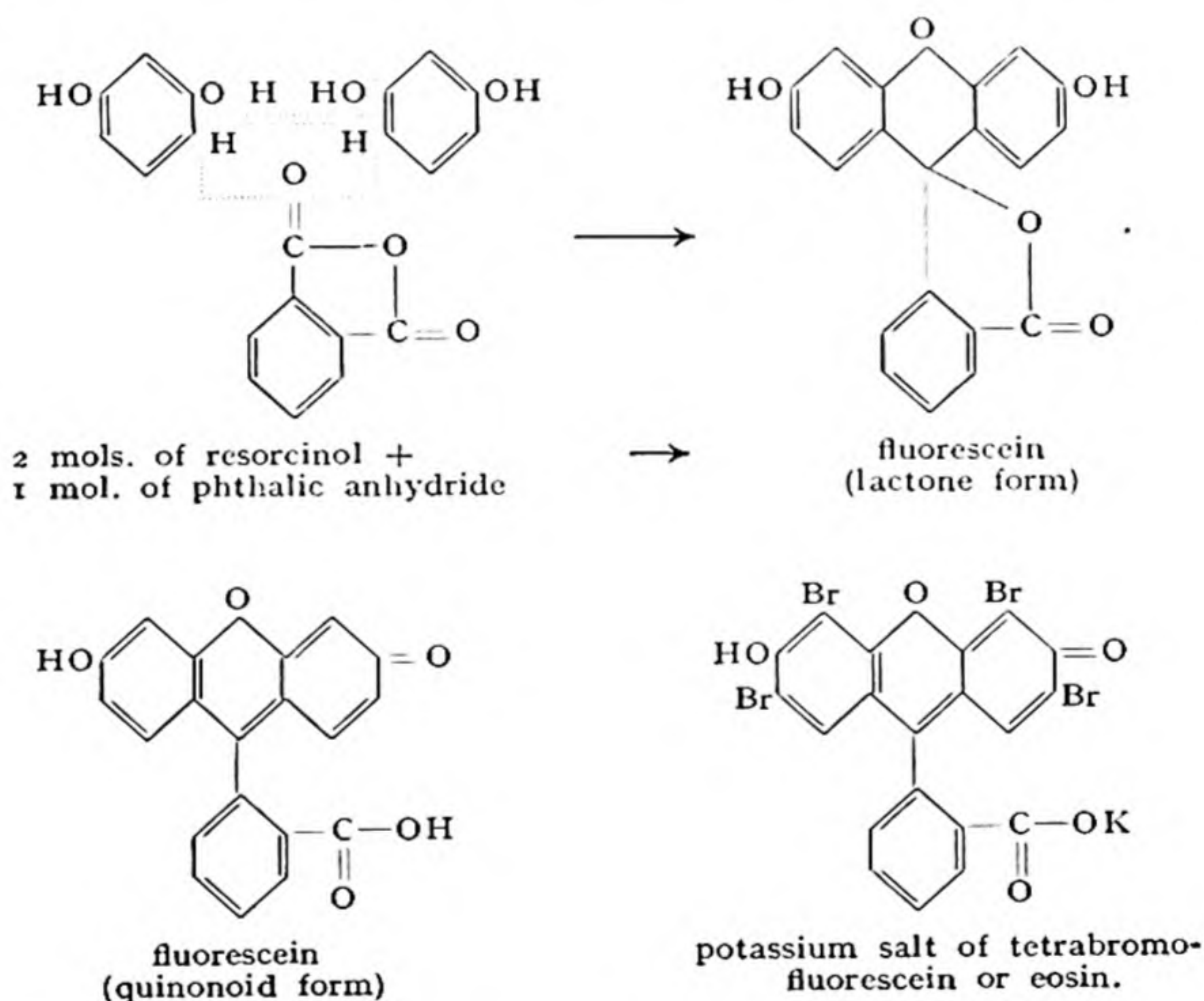
Thus it is assumed that the deep red colour of the sodium salt of phenolphthalein is connected with the presence of a quinonoid group in the molecule. In agreement with this idea is the fact that a coloured methyl ester of phenolphthalein derived from I is known and an isomeric colourless methyl ether derived from II.

As by-product in the preparation of phenolphthalein, there is produced a compound containing one molecule of water less than phenolphthalein in which the two phenol residues are condensed with phthalic anhydride in the *ortho*-positions. This compound, which is insoluble in alkalis, is called *fluorane* and contains a γ -or *1,4-pyrone* ring (325).



Fluorescein or *resorcinolphthalein* is prepared by heating together resorcinol and phthalic anhydride to 210° in presence of sulphuric acid as a dehydrating agent. Because of its powerful yellowish green fluorescence in alkaline solution, the formation of this and similar substances is a very sensitive test for phthalic anhydride (and therefore also for phthalic acid) and other 1,2-dicarboxylic acids like succinic acid or resorcinol.

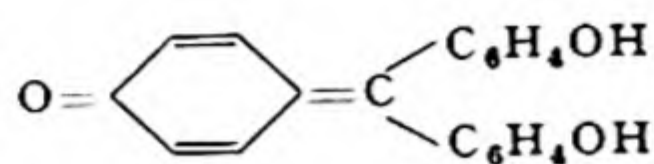
Eosin is the potassium derivative of tetrabromofluorescein and is produced by brominating fluorescein:



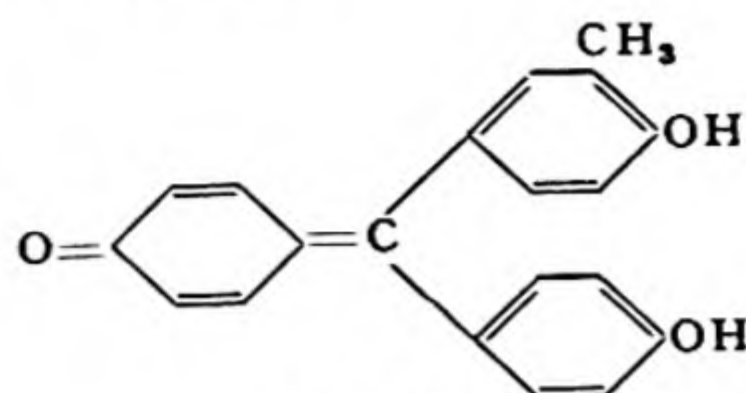
Eosin may be used for dyeing wool, silk and cotton.

The *Aurins* or *rosolic acid dyes* are hydroxy-derivatives of triphenylmethane. *Rosolic acid*, which is produced by diazotising leucaniline with nitrous acid and warming the solution, is not used as a dyestuff but finds application as an indicator; the free acid is yellow and its alkali salts violet in colour.

Aurin, a yellowish brown substance, which dissolves in alkalis with a magenta colour, can be obtained from pararosaniline via the diazonium compound or by heating phenol with oxalic acid in sulphuric acid:



Aurin

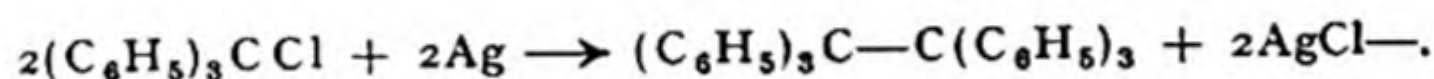


Rosolic acid

Triphenylmethyl and other related free radicals

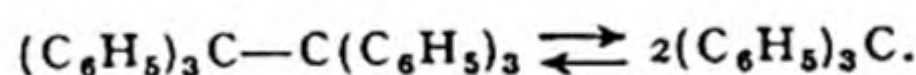
277. By a free radical is meant a compound in which the valency of an element is one lower than corresponds with its position in the periodic table.

The simplest radical containing trivalent carbon is CH_3 , methyl, which has already been discussed in 89. Long before the discovery of free methyl by PANETH (1929), GOMBERG discovered *triphenylmethyl* in 1900. He wished to prepare hexaphenylethane from triphenylchloromethane by a WURTZ-FITTIG synthesis and he finally succeeded by using finely divided silver or copper with the complete exclusion of oxygen:



The crystalline, colourless hexaphenylethane gave deep yellow coloured solutions, which reacted spontaneously with bromine or iodine with the formation of $(\text{C}_6\text{H}_5)_3\text{CBr}$ and $(\text{C}_6\text{H}_5)_3\text{Cl}$, respectively, or with oxygen with the formation of $(\text{C}_6\text{H}_5)_3\text{COOC}(\text{C}_6\text{H}_5)_3$ and decolourisation of the solution.

The radical triphenylmethyl is present in the yellow solution:



From cryoscopic determinations it appears that hexaphenylethane is dissociated to the extent of 2 % in benzene solution.

The degree of dissociation of such compounds can also be determined by comparing the absorption of light of solutions of different concentrations. When a non-dissociating coloured compound is present, it is found that solutions of different concentrations show the same degree of absorption of light if the thickness of the layer of liquid measured is inversely proportional to the concentration (BEER's law, see also 13.) BEER's law no longer holds for substances which dissociate, because the degree of dissociation alters with the dilution. In this case the degree of dissociation can be calculated from absorption measurements.

In this way ZIEGLER has determined the equilibrium constant for the equilibrium $(\text{C}_6\text{H}_5)_3\text{C}-\text{C}(\text{C}_6\text{H}_5)_3 \rightleftharpoons 2(\text{C}_6\text{H}_5)_3\text{C}$, in various solvents and at different temperatures. From the change in the equilibrium constant with temperature, it is possible to calculate by means of the VAN 'T HOFF — LE CHATELIER law, the thermal effect of the reaction, *i.e.* the heat of disso-

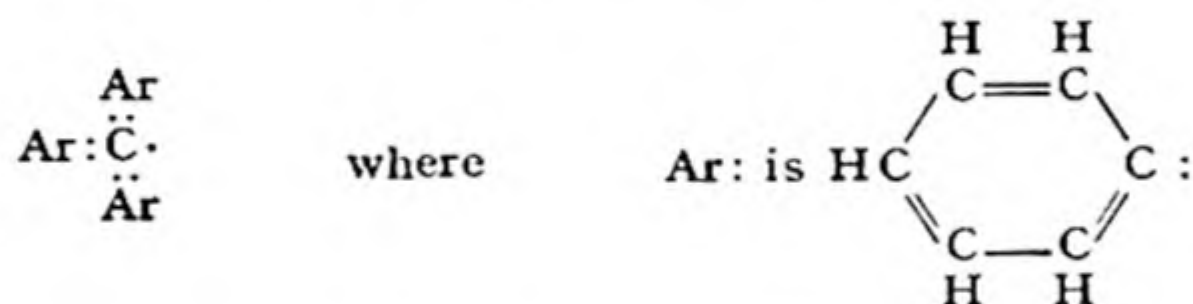
ciation; this appears to be about 11 kcal per gram molecule and expresses the energy necessary to break the C—C bond in hexaphenylethane. Hence this is much lower than the energy value of the C—C bond in $\text{H}_3\text{C—CH}_3$ (see 88).

When the phenyl groups in hexaphenylethane are replaced by diphenyl groups $\text{C}_6\text{H}_5\text{—C}_6\text{H}_4\text{—}$, the degree of dissociation of the compounds produced increases with the number of diphenyl groups in the molecule. Hexadiphenylethane does not exist, since it is completely dissociated into tri-diphenylmethyl $(\text{C}_6\text{H}_5\text{C}_6\text{H}_4)_3\text{C—}$, which is intensely coloured even in the solid state (SCHLENK).

Free radicals are all extremely reactive. They are decomposed by light and possess powers of addition. On reduction, triphenylmethane or one of its derivatives is produced.

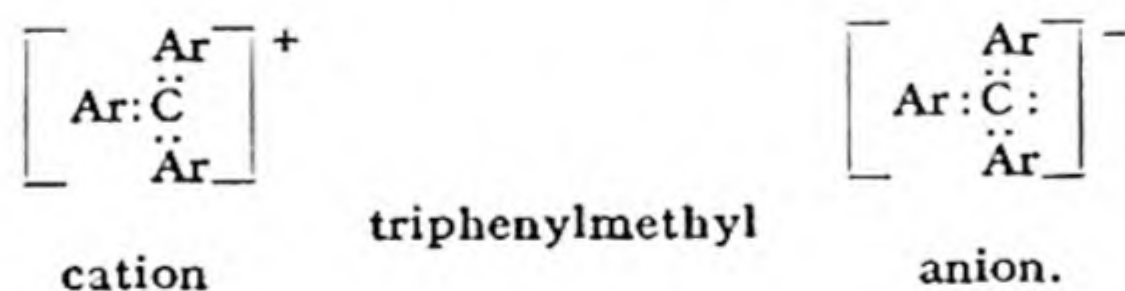
By the action of finely divided sodium on triphenylmethyl dissolved in benzene, there is produced a red compound $(\text{C}_6\text{H}_5)_3\text{CNa}$, in which the group $(\text{C}_6\text{H}_5)_3\text{C}$ must be regarded as an anion (SCHLENK).

It was mentioned in 275 that a solution of triphenylmethyl chloride in liquid sulphur dioxide shows electrical conductivity, and the $(\text{C}_6\text{H}_5)_3\text{C}$ group appears to be the cation. The electronic configuration of triphenylmethyl can be represented as follows:



The triphenylmethyl carbon atom possesses an unshared electron.

The free radical triphenylmethyl is an electrically neutral molecule. The conversion of this molecule into an anion or into a cation is represented as follows:

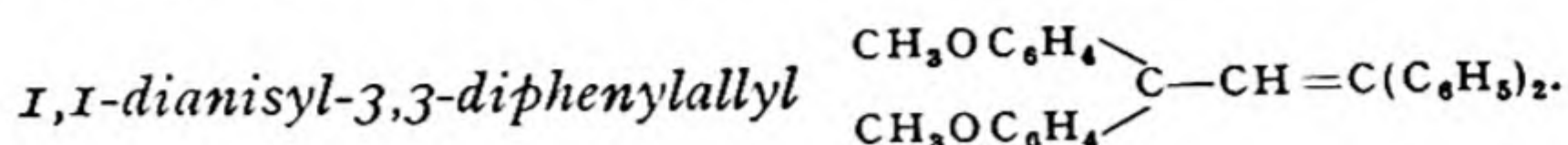


A solution of hexaphenylethane in liquid sulphur dioxide conducts electricity. It is concluded that the triphenylmethyl group is present in such a solution as a cation (carbonium ion), because the absorption spectrum of the solution is similar to that of a solution of triphenylmethyl bromide in liquid sulphur dioxide, but different from that of a solution of triphenylmethyl in ether; in the ethereal solution, which is nonconducting, the triphenylmethyl radical is not converted into an ionic form.

In the conversion of the triphenylmethyl radical into a triphenylmethyl cation the unshared electron from the triphenylmethyl is taken up by the sulphur dioxide.

According to magnetic theory, compounds possessing an unshared electron in the molecule should be paramagnetic. Paramagnetic susceptibility has indeed been observed with tri-biphenyl-methyl both in the solid state and in solution.

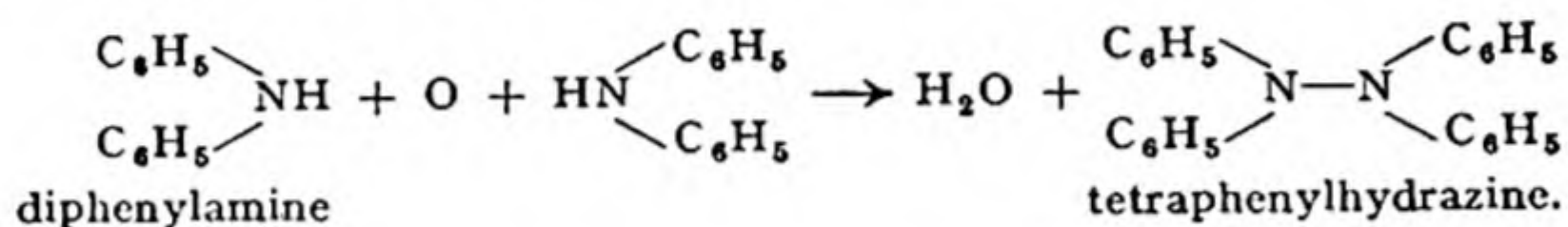
Radicals are also known in which the trivalent carbon atom is attached to two phenyl groups and a substituted vinyl group, *e.g.*:



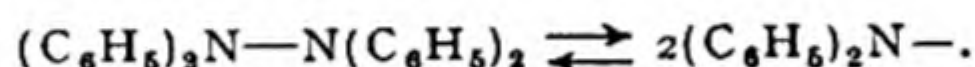
A solution of this compound in benzene contains only the mono-molecular form of the compound and is therefore deep green in colour.

Radicals with divalent nitrogen

278. These compounds were discovered by WIELAND (1911). The analogue of hexaphenylethane is *tetraphenylhydrazine*, which is obtained by oxidising diphenylamine dissolved in acetone with potassium permanganate at a low temperature:



This compound partially dissociates in solution in toluene at 90° as follows:¹



As a result of this dissociation the solution assumes a green colour due to the intensely coloured radicals $\text{R}_2\text{N} \cdot$. In these compounds the degree of dissociation is increased by substituents in the phenyl nuclei such as methyl in the *ortho*-position or methoxyl or dimethylamino-groups in the *para*-position.

Tetra-(p-dimethylaminophenyl) hydrazine $[(\text{CH}_3)_2\text{N}-\text{C}_6\text{H}_4-]_2\text{N}-\text{N}[-\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2]_2$ is dissociated to the extent of about 20 % in nitrobenzene solution and to the extent of about 10 % in benzene solution, both at 5°.

The solution of *tetra-anisylhydrazine* $(\text{CH}_3\text{OC}_6\text{H}_4)_2\text{N}-\text{N}(\text{C}_6\text{H}_4\text{OCH}_3)_2$ is colourless at ordinary temperatures and becomes deep green on warming due to dissociation occurring. On cooling, re-association takes place and the solution becomes colourless again. These radicals are again very reactive and usually unstable. They are not sensitive to oxygen but they add on nitric oxide (NO) spontaneously.

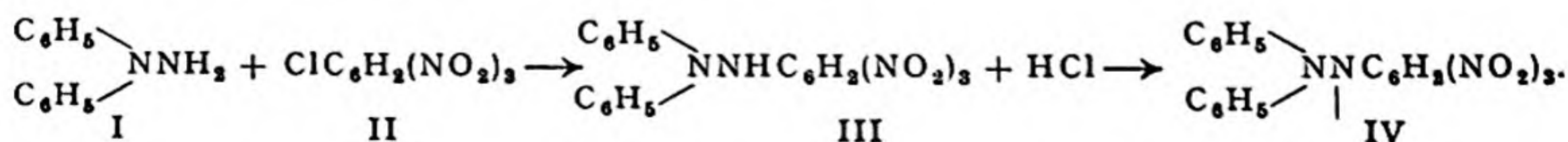
When nitric oxide is passed into a solution of tetraphenylhydrazine, a quantitative yield of *diphenylnitrosamine* is produced $(\text{C}_6\text{H}_5)_2\text{N}-\text{NO}$.

Diphenyltriphenylmethylamine $(\text{C}_6\text{H}_5)_3\text{C}-\text{N}(\text{C}_6\text{H}_5)_2$ is formed with triphenylmethyl.

Free radicals of the type of *triphenylhydrazyl* $(\text{C}_6\text{H}_5)_2\text{N}-\text{N} \cdot -\text{C}_6\text{H}_5$, have been discovered by ST. GOLDSCHMIDT.

1,1-Diphenyl-2-trinitrophenylhydrazyl is produced in the following way.

By the action of asymmetrical diphenylhydrazine (I) on picryl chloride (II), 1,1-diphenyl-2-trinitrophenylhydrazine (III) is obtained:



By oxidation with lead peroxide, the hydrogen atom on the NH-group in III is removed

with the formation of *1,1-diphenyl-2-trinitrophenylhydrazyl* (IV). This compound consists of dark violet crystals. This radical does not associate to the bi-molecular form as is shown by the determination of the paramagnetic susceptibility.

(xvii) HYDROCARBONS WITH CONDENSED BENZENE RINGS

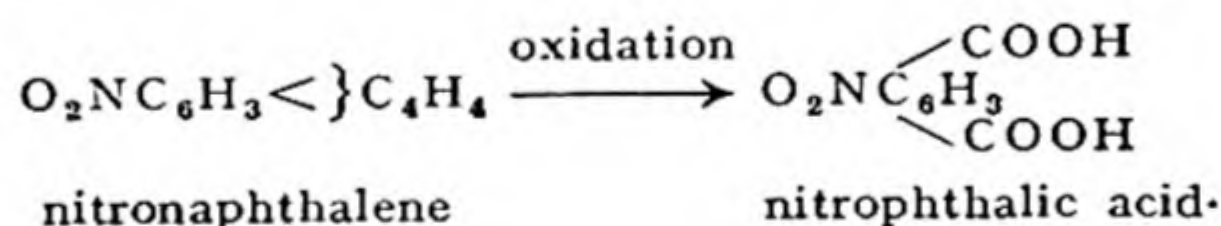
(a) *Naphthalene and its derivatives*

279. *Naphthalene* $C_{10}H_8$ was isolated from coal-tar in 1821 (KIDD); the empirical formula was established in 1826 by FARADAY. This hydrocarbon forms colourless, shining leaflets, melting at 81° . It boils at 218° ; is very volatile (hence its occurrence in coal-gas) and has a characteristic odour; it is very sparingly soluble in water but dissolves readily in many organic solvents.

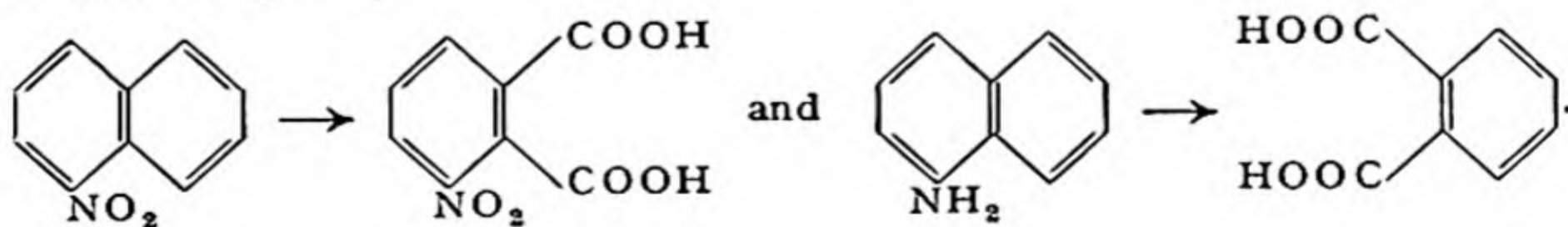
Naphthalene occurs in coal-tar in larger quantities than any other hydrocarbon and is recovered by cooling the carbolic and creosote oil fractions. The crude naphthalene is treated with concentrated sulphuric acid to remove impurities and is then purified by distillation and recrystallisation.

The structure of naphthalene. As will appear in the discussion on the substitution products of naphthalene, the latter shows the properties of an aromatic compound. The structural formula was suggested in 1866 by ERLÉNMEYER on the basis of KEKULÉ's formula for benzene and was proved experimentally in 1869 by GRAEBE. The proof given below is based on the same reasoning as that of GRAEBE but is somewhat simpler (NÖLTING).

Phthalic acid (266) is produced on oxidising naphthalene. From this it follows that the structure may be written as $C_6H_4<\}C_4H_4$, in which the group C_4H_4 is attached to two *ortho*-positions in the benzene nucleus. Similarly, nitronaphthalene is converted into *nitrophthalic acid*. Hence in this case also, the C_4H_4 -group is degraded to two carboxyl groups:



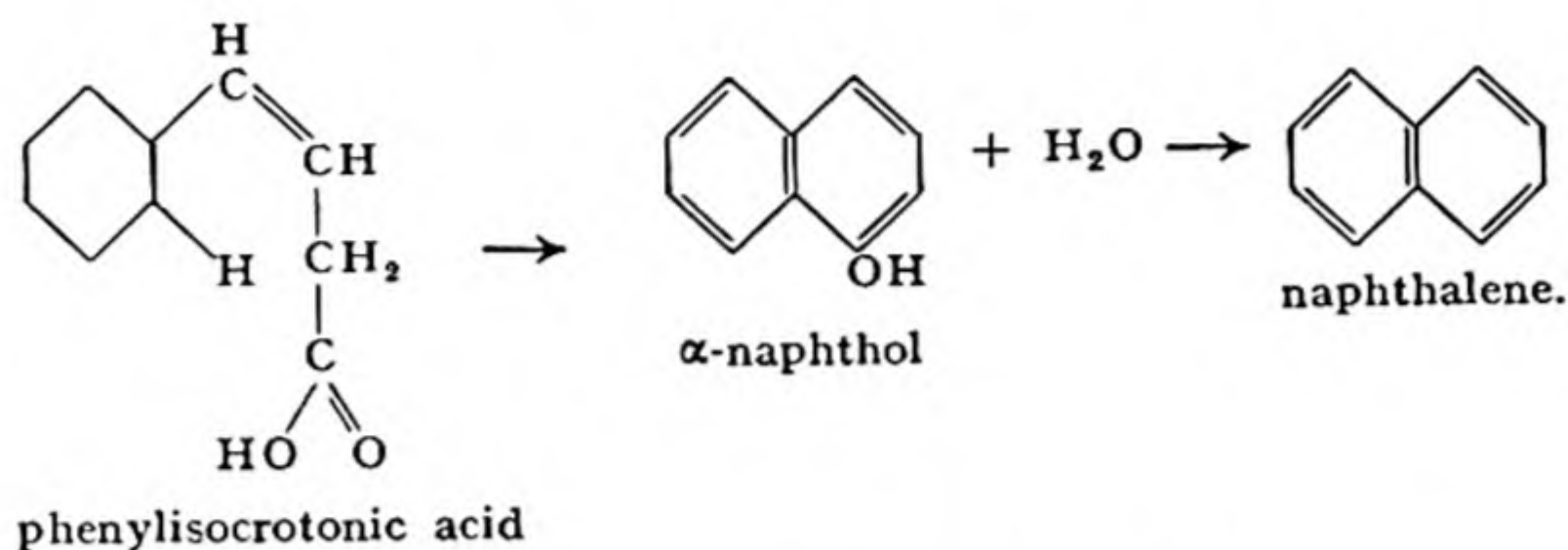
If the nitro-group in nitronaphthalene is reduced and the resultant *aminonaphthalene* (naphthylamine) is oxidised then phthalic acid is again produced. With aminonaphthalene, oxidation commences at the easily oxidisable amino-group:



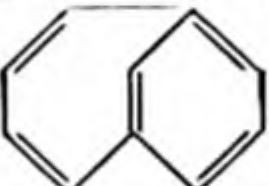
From this it follows, that the C_4H_4 -group with two carbon atoms of the

benzene ring, form a second benzene nucleus, so that the structure of naphthalene must be represented by a formula in which two benzene rings are condensed or fused together at *ortho*-positions.

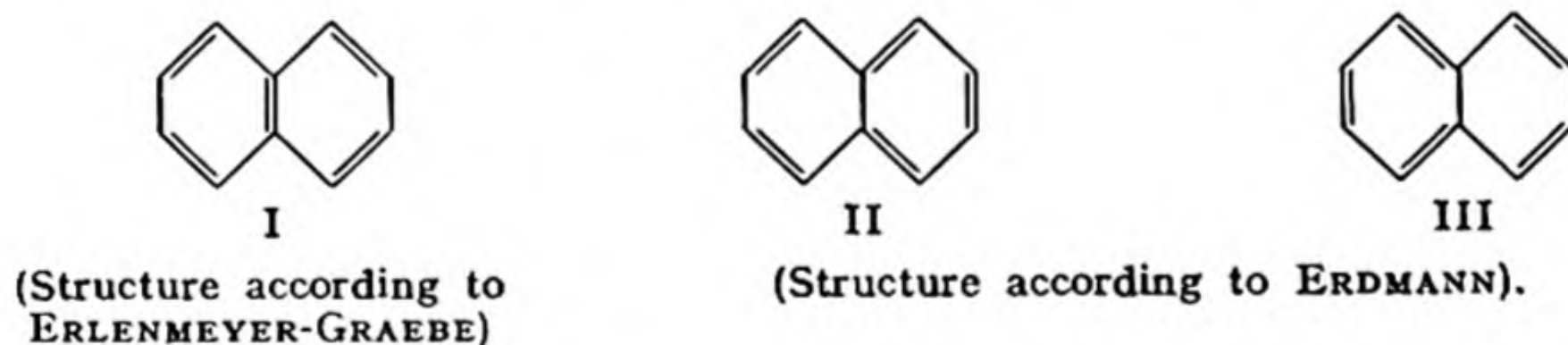
The structure of naphthalene has been confirmed by various syntheses. On heating *3-phenylpropene-2 1-carboxylic acid* (*phenylisocrotonic acid*) a hydroxy-derivative of naphthalene is produced, namely, α -naphthol, from which naphthalene can be produced by distillation with zinc dust:



From the above, it also follows that phthalic acid is an *ortho*-compound, for if it is assumed, for example, that the acid has the meta-structure, then naphthalene

must be represented by , which is not in accordance with the experimental data, because a derivative of benzene would not then be produced by the oxidation of both nitro- and amino-naphthalene.

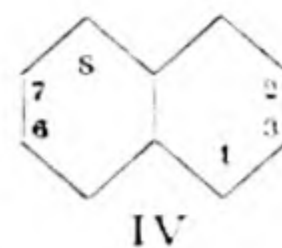
The structure of naphthalene can be represented therefore by three formulae, which differ only in the positions of the double bonds:



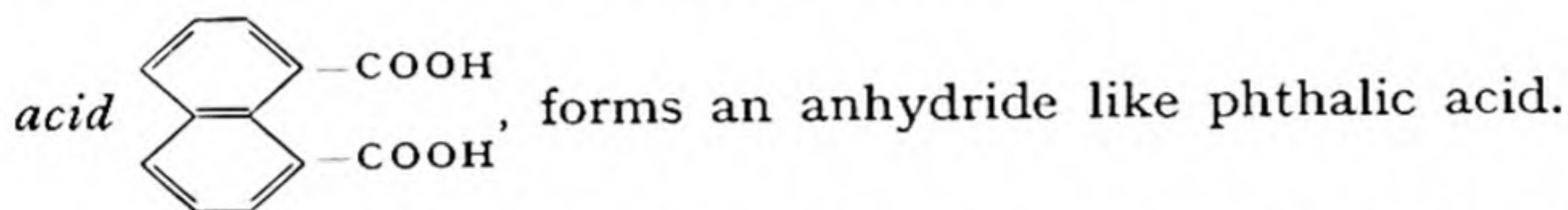
Structure I contains two six-rings in which there are three double and three single bonds as in a benzene ring; in structures II and III only one six-ring has this configuration.

It is now accepted that naphthalene is a mesomeric form, to which the three valency-structures I, II and III, are related (compare 215). In agreement with this idea is the fact that the distances between any two neighbouring carbon atoms in the naphthalene molecule are approximately equal and amount to 1.39 Å. Diacetyl and small amounts of methylglyoxal are formed by the action of ozone on 2,3-dimethylnaphthalene followed by decomposition of the ozonide, which indicates that this dimethylnaphthalene can react in accordance with different valency structures (WIBAUT, VAN DIJK, KAMPSCHMIDT).

280. It makes no difference which formula is accepted for studying isomerism phenomena, since for this purpose, the simplified formula IV, in which the carbon atoms on which substitution may occur are numbered, may be used. Mono-substitution products can occur in two isomeric forms, since the substituent may be attached to one of the carbon atoms 1, 4, 5 or 8, which are directly attached to the carbon atoms common to the two ring systems, or to one of the carbon atoms 2, 3, 6 or 7. In the former case the compounds are known as α -substitution products and in the latter case as β -substitution products. Both groups of carbon atoms are mutually equivalent.



With two like substituents, ten and with dissimilar substituents, fourteen isomers are possible. With three dissimilar substituents the number of isomers is still greater. A 4,5-substitution product is designated also as $\alpha\alpha'$ - and a 3,6-substitution product as $\beta\beta'$ -. Substitution in positions 4 and 5 or 1 and 8 is also known as *peri*-substitution. In some respects this shows similarity to *ortho*-substitution, for example *peri-naphthalene dicarboxylic acid*



Oxidation of naphthalene derivatives, is an important method used for their *orientation*. If a disubstituted phthalic acid is produced, then the substituents present in the acid occur in the same benzene ring in the naphthalene derivative. Hence, if the positions of these substituents in the phthalic acid are known, their positions in the naphthalene derivative are known also.

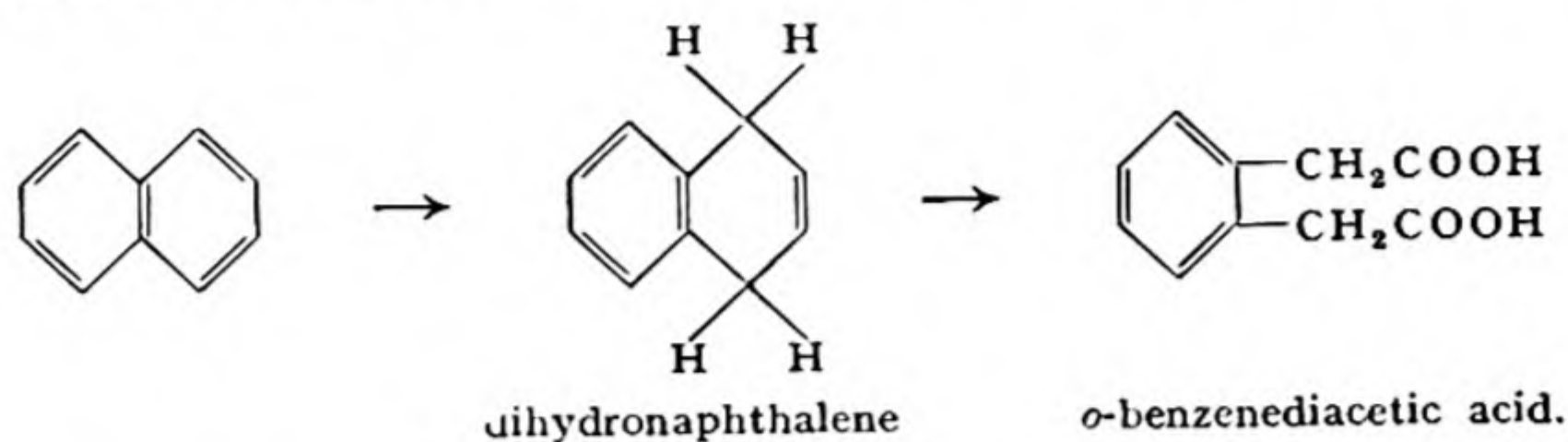
Further, the same method is used as for the relative orientation of benzene derivatives (217), *i.e.* the conversion of compounds with substituents in unidentified positions into compounds in which the positions of the substituents are known. On account of the large number of isomers, orientation in naphthalene derivatives is sometimes difficult, and therefore, in a number of cases the positions of the substituents are still not known with certainty.

Homologues of naphthalene. Methyl- and ethyl-naphthalene can be obtained by the methods of FITTIG or of FRIEDEL and CRAFTS (218).

α -Methylnaphthalene is a liquid boiling at 240-242°. β -Methylnaphthalene melts at 32°; both occur in coal-tar. On oxidation they give α - and β -naphthoic acid, respectively, which are similar in properties to benzoic acid. These acids are converted into naphthalene by distillation with lime.

Hydrogenated naphthalenes. Naphthalene can be hydrogenated more easily than benzene. All the steps in the hydrogenation from dihydronaphthalene to decahydronaphthalene are known, each successive compound having

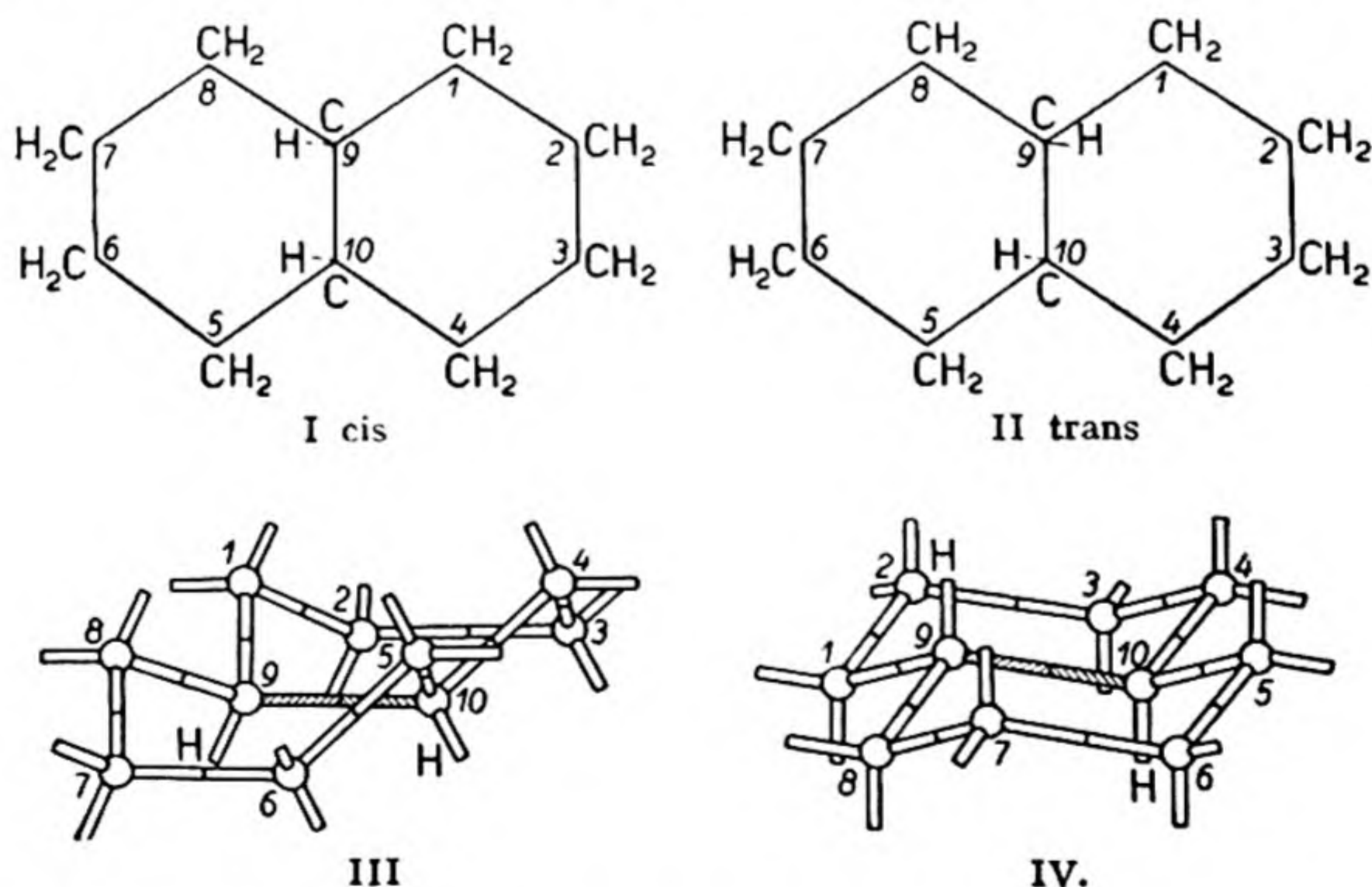
two more atoms of hydrogen than its predecessor. 1,4-*Dihydronaphthalene* $C_{10}H_{10}$, is produced by the action of sodium and alcohol on naphthalene. On oxidation it is converted into *o*-benzenediacetic acid:



From this it follows that the hydrogen in positions 1 and 4 is added on to the system of conjugated double bonds.

Tetrahydro- and *decahydronaphthalene* (commercial names *tetralin* and *decalin*) are prepared commercially by hydrogenating naphthalene with hydrogen under a pressure of 10–15 atmospheres in the presence of a finely divided nickel catalyst. They are used as solvents.

Decahydronaphthalene exists in two stereoisomeric forms, both of which occur in the crude hydrogenation product from which they can be isolated by fractional distillation (W. HÜCKEL). *cis*-Decahydronaphthalene boils at 193° and has $d_4^{20} = 0.898$. *trans*-Decahydronaphthalene boils at 185° and has $d_4^{20} = 0.871$. The molecular heat of combustion is 1497 kcal for the *trans*-isomer and 1500 kcal. for the *cis*-isomer. When MOHR models are constructed with strain-free rings (288) the carbon atoms in both (cyclohexane) rings do not then lie in a plane; it appears that two space models are possible. In the *cis*-form the two hydrogen atoms attached to the two carbon atoms 9 and 10 common to both rings, lie in the same segment in space.



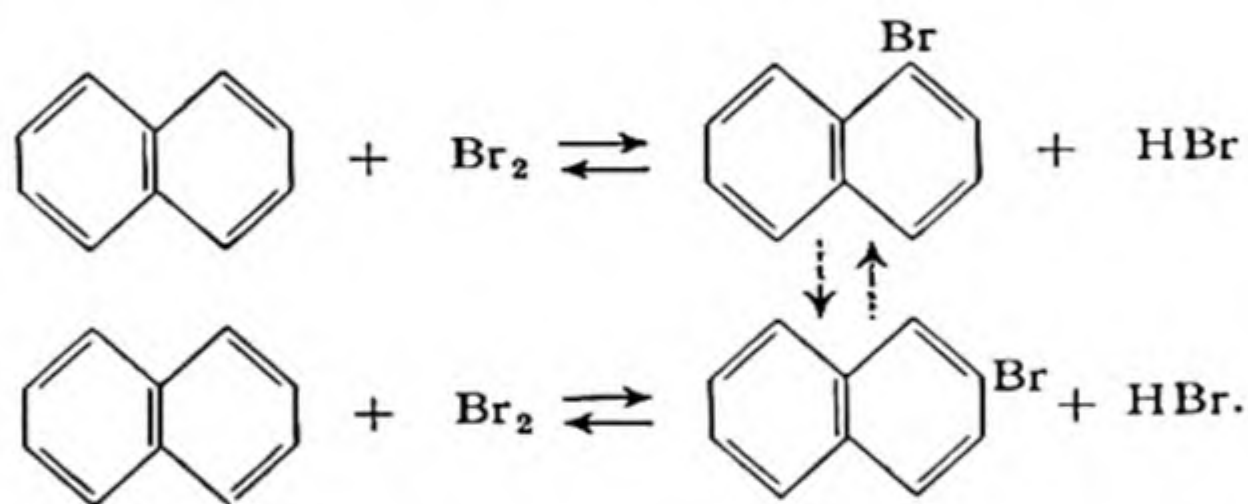
In the *trans*-isomer these hydrogen atoms lie in different segments; the position of the two cyclohexane rings (formed by carbon atoms 1, 2, 3, 4, 10 and 9 and 5, 6, 7,

8, 9 and 10) with respect to each other is different in these two configurations. Figs. III and IV represent perspective drawings for the *cis*- and *trans*-models respectively, in which the bond between carbon atoms 9 and 10 is shaded.

Substitution products of naphthalene

281. From recent investigations it has been found that the course of the bromination and the chlorination of naphthalene is influenced to a considerable extent by temperature and by particular catalysts (WIBAUT, SUYVER, SIXMA, BLOEM). When an excess of bromine is allowed to react with molten naphthalene at temperatures between 100° and 200° , the main product is *1-bromonaphthalene* along with a few percent. of 2-bromonaphthalene.

In the bromination of naphthalene vapour, the formation of 2-bromonaphthalene increases rapidly in the temperature range between 350° and 500° ; above 500° equal quantities of 1- and 2-bromonaphthalenes are formed and under these conditions the isomeric mono-bromonaphthalenes are not converted one into the other. This is the case, however, when the bromination is carried out with the aid of ferric bromide or chloride catalysts when the formation of both 1- and 2-bromonaphthalene is reversible:



As a result of this reversible bromination, an equilibrium is set up between 1- and 2-bromonaphthalene, the mixture containing about 60% of the latter; the equilibrium ratio is only slightly influenced by the temperature.

Therefore in bromination with ferric chloride as a catalyst 60% of 2-bromonaphthalene is formed.

In chlorinations carried out in presence of a little iodine as catalyst, the chief product is 1-chloronaphthalene along with a little 2-chloronaphthalene, the amount of the latter increasing with temperature. The halogen atom in the monochloro- and bromo-naphthalenes is rather more mobile than that in mono-chloro- or mono-bromobenzene. They are not affected, however, by boiling with dilute caustic soda.

Mono-nitronaphthalene $\text{C}_{10}\text{H}_7\text{NO}_2$, m.p. 61° , is produced by the action of concentrated nitric acid on naphthalene. On reduction of this nitrophthalene a naphthylamine is produced, which may be converted into the same naphthol as is obtained from phenylisocrotonic acid (279). From this it follows that the nitro-group is situated in the α -position.

α -Nitronaphthalene is important for the orientation of mono-substitution products since the nitro-group can be replaced by various other groups via

the amino- and diazonium groups. If it is known that a mono-substituted naphthalene is an α -compound, its isomer must be a β -compound.

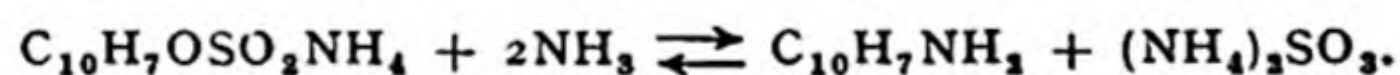
β -Nitronaphthalene is produced in small quantities in the nitration of naphthalene (FIERZ DAVID and SPONAGEL) but is prepared by a roundabout method. It melts at 79° .

Mono-sulphonic acids of naphthalene. α -Naphthalenesulphonic acid $C_{10}H_7SO_3H$, is produced by heating naphthalene with concentrated sulphuric acid at 80° . The β -acid is produced as the chief product by heating this mixture to 160° . Both isomers are interconvertible when treated in this way. At 160° the equilibrium mixture is composed mainly of the β -isomer.

Naphthols $C_{10}H_7OH$ are produced by fusing the sulphonic acids with potash. α -Naphthol melts at 95° and boils at 282° and like β -naphthol it occurs in coal-tar. β -Naphthol melts at 122° and boils at 288° . Both are soluble in caustic potash solution. The naphthols are very similar in properties to the phenols (229). The hydroxyl group can be replaced more easily in naphthols than in phenol.

Decahydronaphthols (decalols) are produced by the catalytic hydrogenation of α - or β -naphthol. From stereochemical models it follows that four stereoisomeric decahydronaphthols, each of which consists of a racemic mixture, can be produced from one naphthol. Indeed HÜCKEL has found four racemic decalols related to β -naphthol (compare the figures on page 456).

Mono-aminonaphthalenes or naphthylamines $C_{10}H_7NH_2$. α -Naphthylamine can be prepared by reducing α -nitronaphthalene. β -Naphthylamine is prepared by heating β -naphthol with an aqueous solution of ammonium sulphite and ammonia at 100 – 150° (BUCHERER). In this reaction the salt of a naphtholsulphite ester, which changes over into β -naphthylamine and sulphite, is produced as an intermediate product. This reaction is reversible thus:

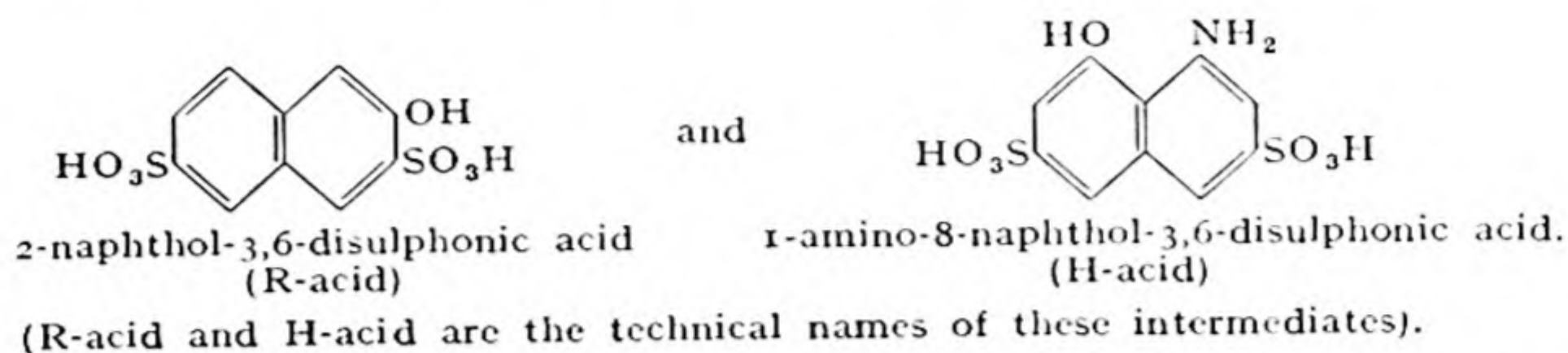


α -Naphthylamine melts at 50° and has an unpleasant odour. β -Naphthylamine melts at 112° and is practically odourless. Salts of α -naphthylamine give a blue precipitate with ferric chloride and other oxidising agents, salts of β -naphthylamine do not react with these reagents.

Various isomeric naphthylaminesulphonic acids are produced by sulphonating the naphthylamines. *1-Naphthylamine-4-sulphonic acid* or naphthionic acid (see 255) is produced in this way from α -naphthylamine; on heating the reaction mixture for a long time, this acid is converted into *1-naphthylamine-6-sulphonic acid*.

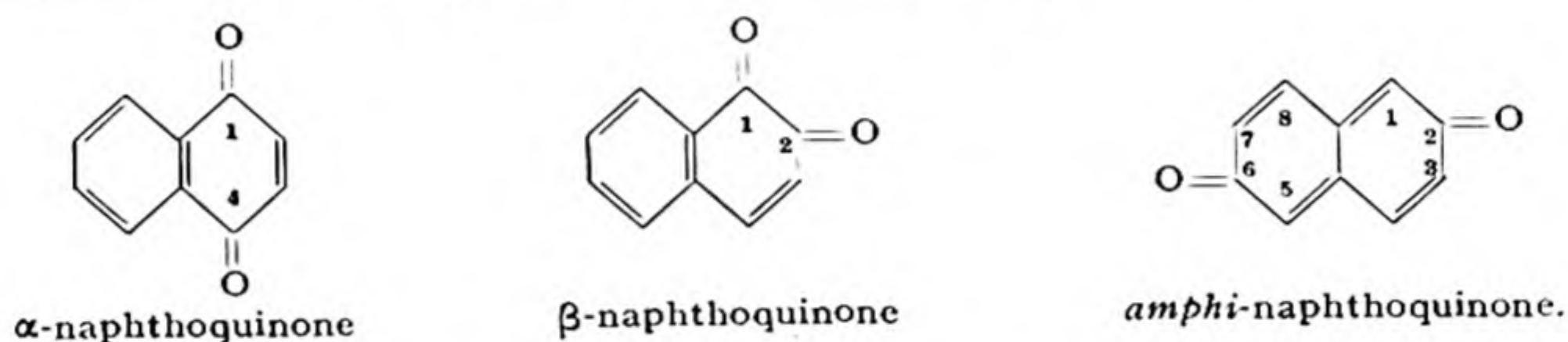
The naphthols, naphthylamines and the sulphonic acids of naphthalene

and its derivatives are important primary products for the manufacture of dyestuffs. As examples may be mentioned the following sulphonic acids containing a hydroxyl group and an amino- and a hydroxyl group, respectively:

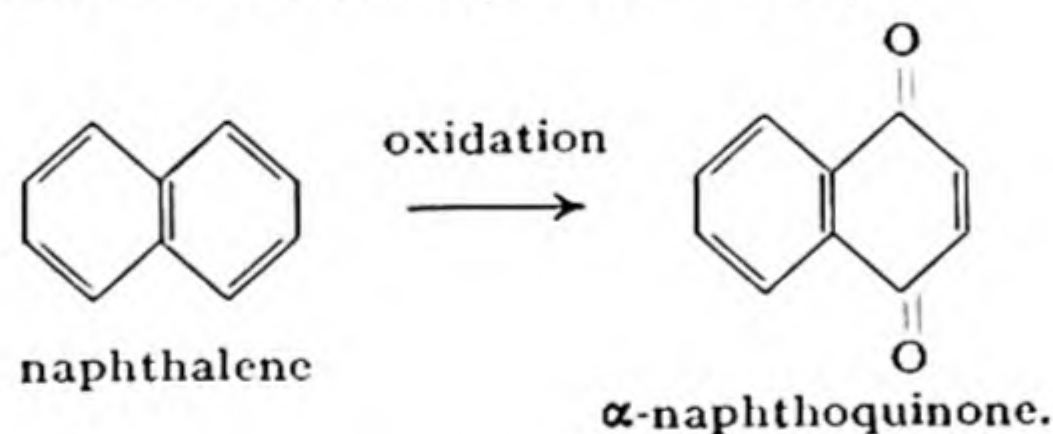


These, and other substituted naphthalenesulphonic acids are used in the preparation of azo-dyestuffs.

Naphthoquinones $C_{10}H_6O_2$. Besides α - and β -naphthoquinones, *amphi*- or 2,6-naphthoquinone is also known. These quinones can be prepared, in general, in the same way as benzoquinones (233):



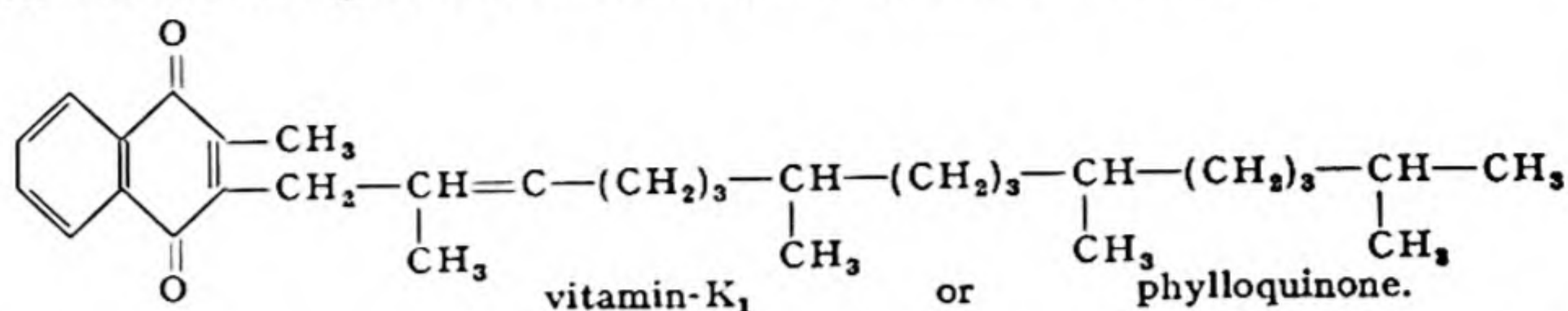
α -Naphthoquinone is produced by oxidising various α -derivatives or 1,4-derivatives of naphthalene. It is prepared, however, by the oxidation of naphthalene with a boiling solution of chromic acid in glacial acetic acid (compare the preparation of anthraquinone 282):



It is a yellow, crystalline compound, m.p. 125° , which is volatile in steam and possesses a penetrating odour. On oxidation it gives phthalic acid. In this way it is proved that both oxygen atoms are attached to the same benzene nucleus, *i.e.* there is only one quinonoid ring in α -naphthoquinone. With hydroxylamine a dioxime is formed.

The position of other disubstituted naphthalenes can be determined from the structure of α -naphthoquinone. If this quinone is produced from a particular derivative by oxidation, with the elimination of the two substituents, then the original substituents are present in positions 1 and 4.

Various dyestuffs occur in the vegetable kingdom which are derivatives of α -naphthoquinone. Another important derivative is *vitamin-K₁* or *phylloquinone* (see 306) to which the following structure is assigned (DOISY; FIESER):



Thus this compound is an α -naphthoquinone carrying a methyl group and a phytyl group (see 95) as substituents.

β -Naphthoquinone is produced by oxidising 1,2-aminonaphthol. It crystallises in red needles, m.p. 115–120°; it is odourless and not volatile in steam.

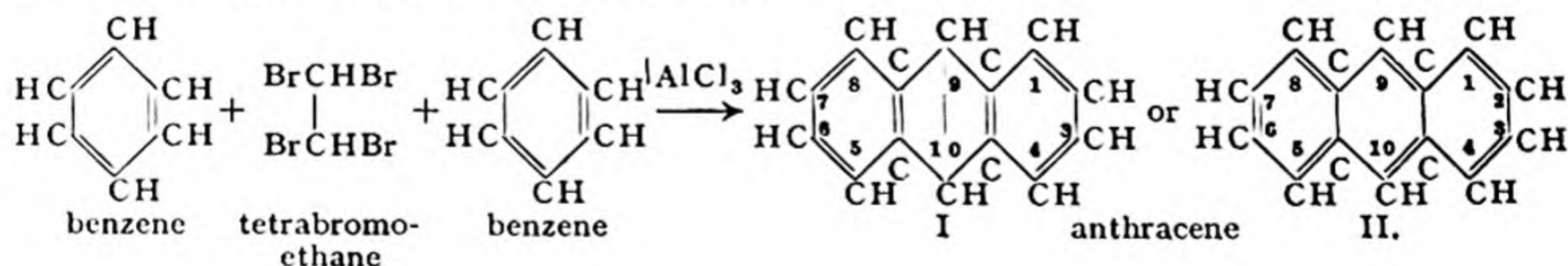
Amphi- or 2,6-naphthoquinone is produced by oxidising 2,6-dihydroxynaphthalene with lead dioxide in benzene solution. It is odourless, non-volatile in steam and crystallises in red needles. Both the benzene nuclei in *amphi*-naphthoquinone have a quinonoid structure. This compound has more powerful oxidising properties than α - and β -naphthoquinone.

(b) Anthracene and its derivatives

282. *Anthracene* C₁₄H₁₀, was discovered in 1832 by DUMAS and LAURENT; this hydrocarbon melts at 218° and boils at 342° and its crystals show a blue fluorescence.

Anthracene occurs in coal-tar to the extent of 0.25–0.45 %. By fractional distillation of anthracene oil (219), a product containing about 50 % of anthracene can be obtained. This product is then distilled with potash to remove carbazole (317); the distillate then consists of anthracene and the isomeric phenanthrene (284), which are separated by making use of the difference in solubility in crude pyridine oils. The anthracene is eventually purified by recrystallisation.

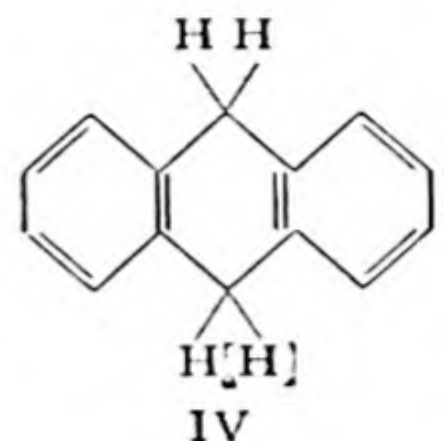
The *structure of anthracene* was established mainly by GRAEBE and LIEBERMANN on the basis of its relationship with anthraquinone and was confirmed by synthesis from benzene and tetrabromoethane in presence of aluminium chloride (ANSCHUTZ):



In formula I carbon atoms 9 and 10 are joined by a valency bond, which is difficult to explain when the distance between these carbon atoms is taken into consideration, therefore formula II is preferred. Mesomerism between various valency structures (215) is now accepted for anthracene. All the substitution products of anthracene can be represented by the simplified formula III.

It may be seen that three mono-substitution products are possible, viz. with substituents in positions 1=4=5=8, 2=3=6=7, and 9=10. Fifteen di-substitution products are possible when the substituents are identical.

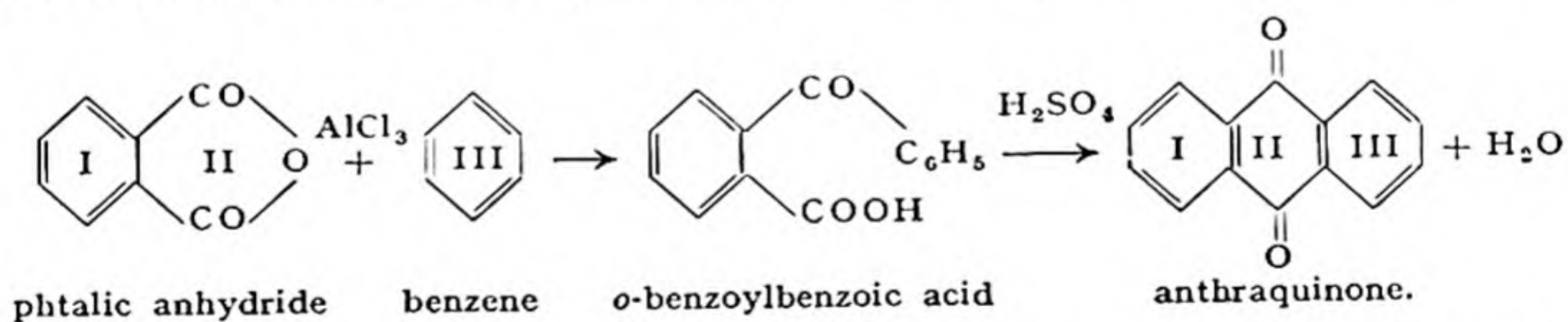
Some reactions of anthracene take place preferentially on carbon atoms 9 and 10. Reduction with sodium amalgam gives 9,10-dihydroanthracene (IV).



This substance is very easily produced also by catalytic reduction but is rapidly reduced still further (SCHROETER).

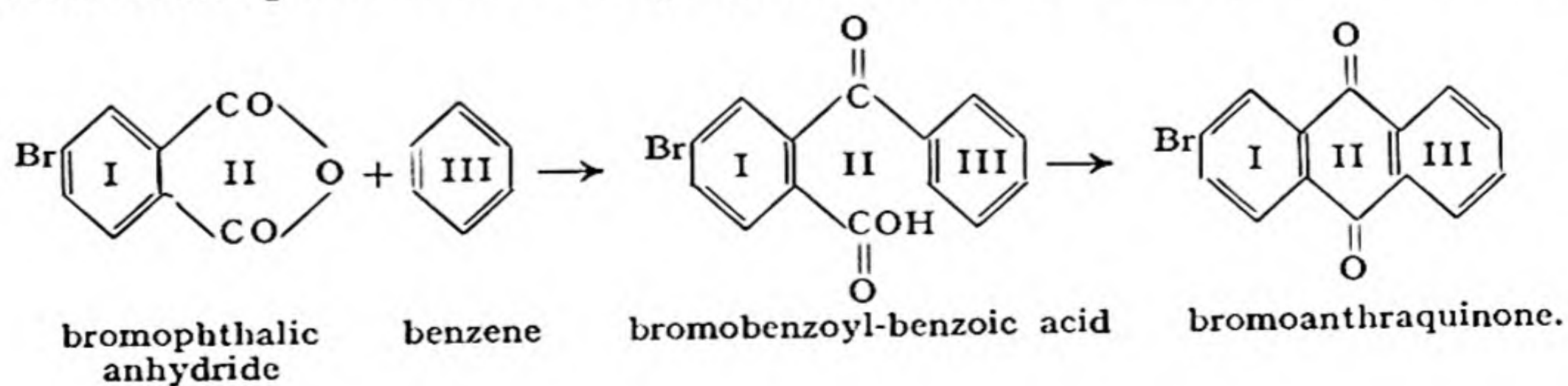
Anthraquinone $C_{14}H_8O_2$, is produced when 9,10-dihydroanthracene is oxidised with chromic acid. This important derivative of anthracene was first obtained by LAURENT by the interaction of nitric acid on anthracene (1840). It is prepared by the action of sodium bichromate and sulphuric acid on anthracene. The structure of anthraquinone is proved by the following syntheses.

Phthalic anhydride and benzene in the presence of aluminium chloride interact to form *o*-benzoylbenzoic acid, which is converted quantitatively into anthraquinone and water by treatment with concentrated sulphuric acid. This method of making anthraquinone is also used on a technical scale:

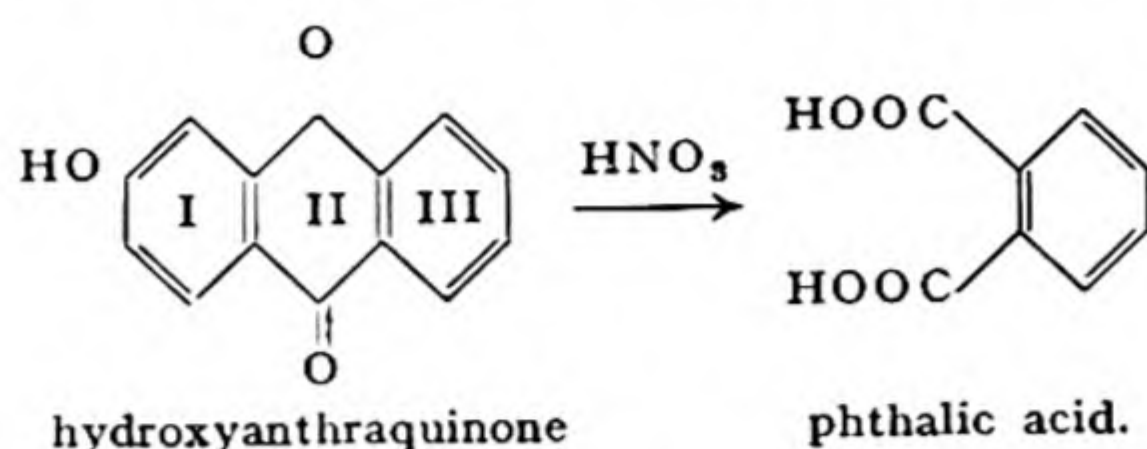


From the above synthesis it follows that rings I and II are condensed in *ortho* positions. Proof that this is also the case for rings II and III is as follows.

A *bromoanthraquinone* can be prepared from 4-bromophthalic acid:



By the action of potash, the bromine atom in the bromoanthraquinone can be replaced by hydroxyl and when the resultant *hydroxyanthraquinone* is oxidised by nitric acid, phthalic acid is produced:

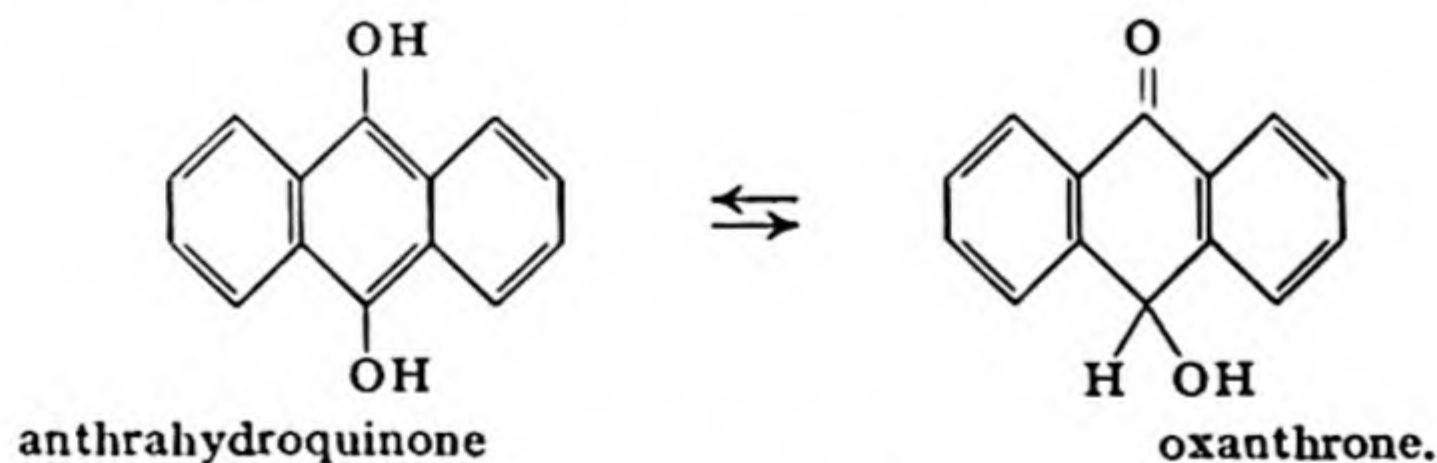


The benzene ring in the phthalic acid so obtained, is derived from ring III of the bromoanthraquinone, so that in ring III also the two carbonyl groups are attached in *ortho*-positions, (compare the proof of the structure of naphthalene 279). Since anthraquinone can be converted into anthracene by powerful reduction, the above provides another proof of the structure of anthracene.

From the structural formula of anthraquinone, it follows that the latter can give rise to two mono-substitution products; both derivatives are known in a large number of cases.

Anthraquinone crystallises from glacial acetic acid in pale yellow crystals melting at 277° ; it sublimes easily at higher temperatures. It is a very stable compound, which is attacked by oxidising agents only with difficulty; it does not possess the characteristic properties of a quinone such as the ability to act as an oxidising agent but shows rather the properties of a diketone. On fusion with potash it forms benzoic acid and gives a dioxime with hydroxylamine.

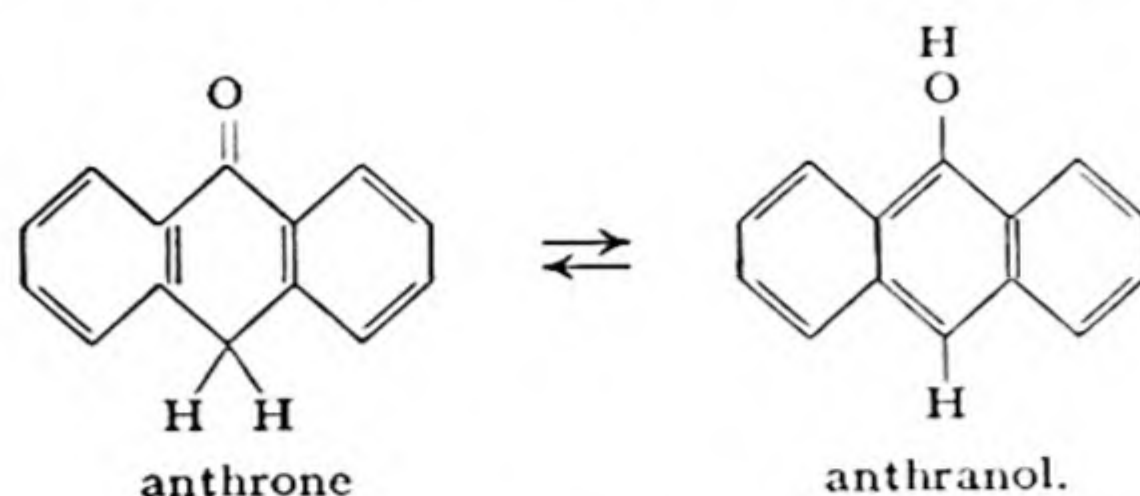
By carefully reducing anthraquinone with zinc dust and caustic soda, the di-sodium derivative of *anthrahydroquinone* is produced. Anthrahydroquinone, m.p. 180° , consists of yellowish brown crystals; the neutral solution shows an intense green fluorescence. It dissolves in alkali with a red colouration; this solution becomes colourless when shaken with air due to the formation of anthraquinone. This is a sensitive reaction for the latter compound.



Oxanthrone is isomeric with anthrahydroquinone. By treating the latter with cold alcoholic hydrochloric acid, about 3 % is converted into oxanthrone and when oxanthrone is treated in the same way, about 97 % is converted into anthrahydroquinone. In other words an equilibrium mixture of the two compounds is produced. Oxanthrone

is a colourless substance melting at 167° . These isomers are examples of tautomeric compounds both of which are stable in the solid state.

Anthrone is produced by reducing anthraquinone with tin and hydrochloric acid. When anthrone is warmed with alkalis it passes into solution and on acidifying the latter, the tautomeric compound *anthranol*, is precipitated:



Anthranol, which shows a deep blue fluorescence in solution, is readily converted into anthrone. Similarly, when anthrone is boiled in acetic acid solution a little is converted into anthranol. Thus anthranol is to be regarded as the enol form of anthrone.

283. Hydroxyanthraquinones. The most important compound in this group is *alizarin* $C_{14}H_8O_4$, a red dyestuff, which was at one time produced on a very large scale from the roots of the madder plant (*rubia tinctorum*).

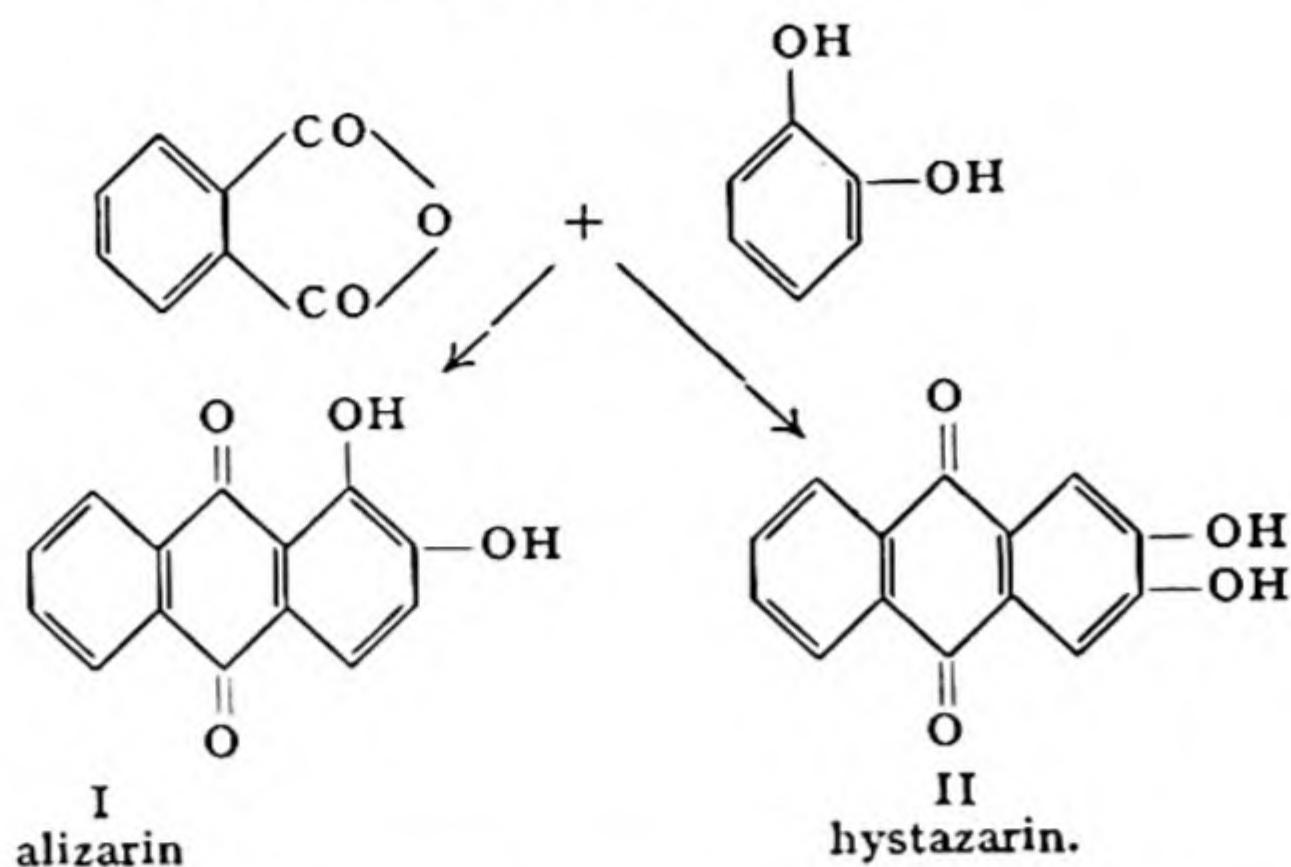
A glucoside (**179**) *ruberythroside* $C_{25}H_{26}O_{13}$, which occurs in these roots, is split up on boiling with dilute sulphuric or hydrochloric acid into alizarin and the disaccharide *primverose*; the latter breaks down further on continued hydrolysis into *d*-glucose and *d*-xylose. The name alizarin is derived from "alizari" the name used for madder in the Middle East.

The structure of *alizarin* was established in 1868 by GRAEBE and LIEBERMANN, who also discovered the first synthesis of this dyestuff. Since that date alizarin has been prepared synthetically from anthraquinone in very large quantities.

Alizarin melts at 289° and sublimes in orange-red needles. It is insoluble in water and sparingly soluble in alcohol. It dissolves in alkalis with an intense blue colour and has therefore the properties of a phenol. It can be acetylated to form a diacetate. On powerful reduction, *e.g.* by distilling alizarin with zinc dust, anthracene is produced, which establishes the carbon skeleton. Since alizarin can be obtained by fusing dibromoanthraquinone with potash, it must be a dihydroxy-derivative of anthraquinone.

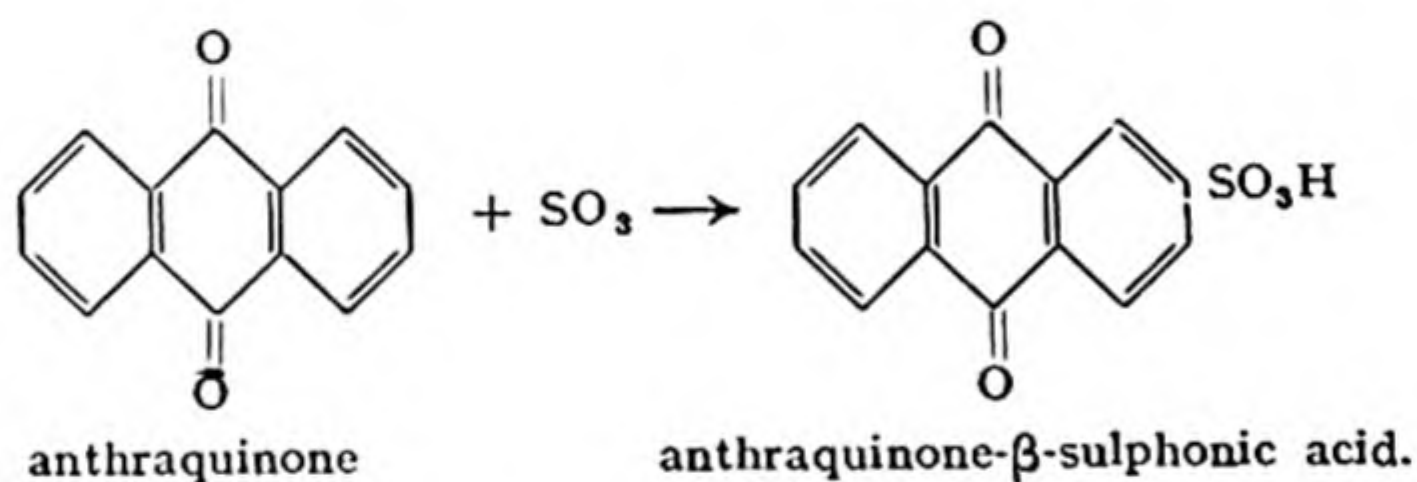
In the oxidation of alizarin, phthalic acid is formed, showing that the molecule contains one benzene nucleus unsubstituted by hydroxyl groups.

On heating phthalic anhydride and catechol to 150° with sulphuric acid, alizarin is produced along with another isomeric dyestuff *hystazarin*. From this it may be concluded that one of the formulae I or II represents alizarin:



On nitrating alizarin, two isomeric mono-nitro-derivatives are obtained, both of which give phthalic acid on oxidation. From this, not only does it follow that the nitro-group is situated in the same benzene nucleus as the hydroxyl groups, but also that structure I must be assigned to alizarin, since only from this structure can two such isomeric-nitration products be obtained.

For the technical preparation of alizarin, anthraquinone is heated to 160° with oleum containing 50 % of sulphur trioxide to form anthraquinone- β -sulphonic acid:



When the sodium salt of this acid is fused with sodium hydroxide and air is passed through the mixture at the same time, the $-\text{SO}_3\text{Na}$ group is replaced by an ONa -group and simultaneously a second NaO -group is introduced into the molecule. The latter reaction takes place much more easily if an oxidising agent like potassium chlorate is added to the melt. The di-sodium derivative of alizarin is formed in this reaction and the dyestuff is obtained by acidifying the product. This process was discovered simultaneously by GRAEBE and LIEBERMANN and by PERKIN.

If the sulphonation of anthraquinone is carried out with fuming sulphuric acid in which mercuric sulphate is present, *anthraquinone- α -sulphonic acid*, which is also used as the starting material for the manufacture of a number of dyestuffs, is practically the sole product (DUNSCHMAN, ILJINSKI, R. E. SCHMIDT). It is found that in the presence of 0.035 % of HgSO_4 , 61 % of β -sulphonic acid and 39 % of α -sulphonic acid are produced; in the presence of 1 % or more of HgSO_4 the ratio is 16.3 % of β -sulphonic acid and 83.7 % of α -sulphonic acid, while in the absence of HgSO_4 98–100 % of the

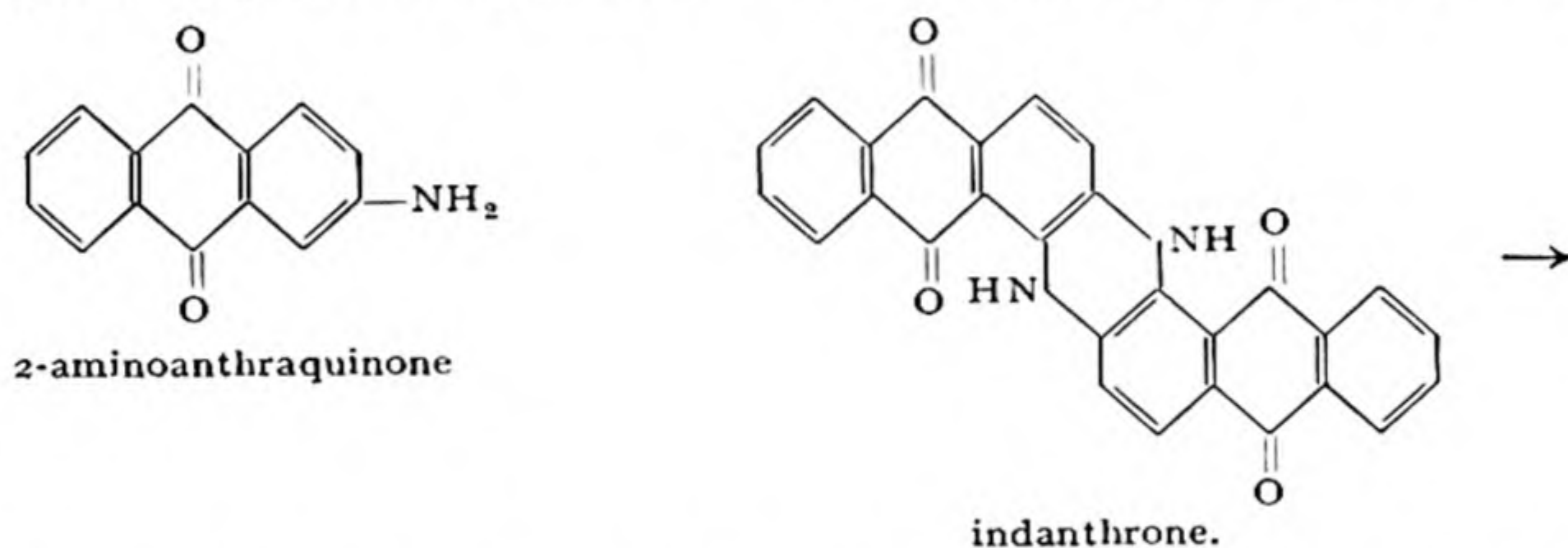
β -acid is produced (WIBAUT and COPPENS). This is a striking example of the directive influence of a catalyst (compare 272, 335).

With metallic oxides, alizarin gives insoluble coloured compounds which are known as "lakes"; they are complex compounds with the metal oxide combined with the *ortho*-orientated hydroxyl groups in the alizarin (compare 255). The colour obtained depends on the oxide used; the compound of alizarin and iron oxide is blackish violet, the chromium oxide compound is bordeaux-red, the calcium compound blue and the tin and aluminium compounds different shades of red (turkey red). In dyeing with alizarin the metal oxides are applied to the cloth beforehand ("mordanting" 252).

Emodins. Derivatives of trihydroxymethylanthraquinones occur in the vegetable kingdom sometimes in the free state and sometimes in the form of glucosides (179) or as methyl ethers; some of these compounds are used as purgatives.

Purpurin, 1,2,4-trihydroxyanthraquinone $C_6H_4(CO)_2C_6H(OH)_3$ is a dyestuff, also occurring in madder root.

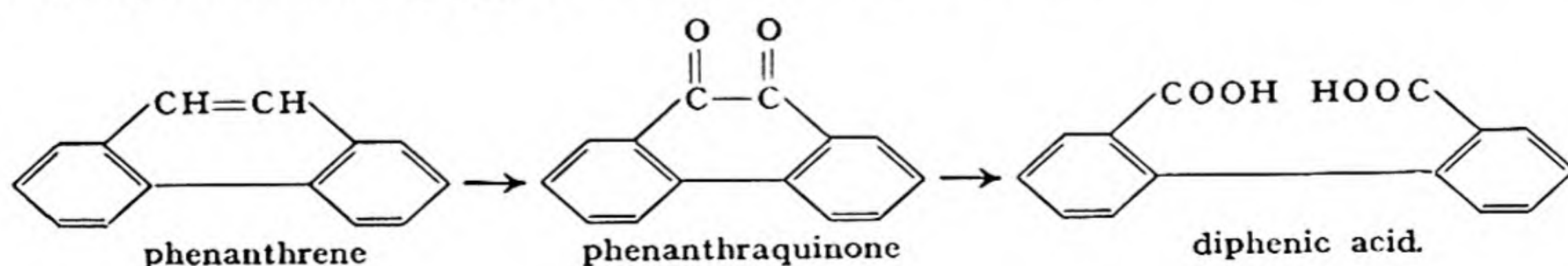
Besides alizarin there are a number of other important dyestuffs in use which are related to anthraquinone; in fact the anthraquinone dyestuffs are of great importance. By fusing 2-aminoanthraquinone with potash *indanthrone* (Indanthrene Blue R) is produced; this is very fast to light and is used as a vat dyestuff (compare 316):



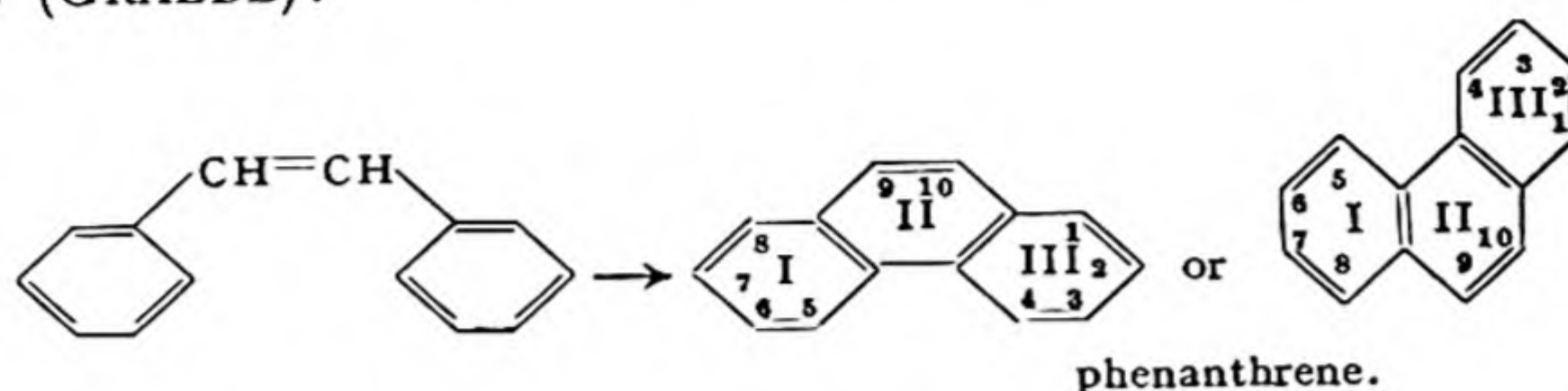
Various other important dyestuffs, *e.g.* *dibenzanthrone* and its derivatives, which are built up of condensed ring systems based on anthraquinone as the starting material, are known besides indanthrone.

(c) *Phenanthrene and its derivatives*

284. *Phenanthrene*, $C_{14}H_{10}$, melts at 101° , boils at 340° and is soluble in many organic solvents; the alcoholic solution fluoresces blue. This hydrocarbon, which is isomeric with anthracene, was isolated from coal-tar simultaneously by FITTIG and OSTERMAYER and by GLASER and GRAEBE (1872). The first mentioned investigators deduced its structure from the following facts. By oxidising phenanthrene, *phenanthraquinone*, $C_{14}H_8O_2$, is produced and from this, diphenic acid (273) is formed on further oxidation:



This structure of phenanthrene is confirmed by the formation of phenanthrene by passing the vapour of 1,2-diphenylethene (stilbene) through a red hot tube (GRAEBE):



In this formula the distribution of single and double bonds in rings I, II and III is the same as in the benzene ring.

It is possible to construct two other formulae, besides the one represented above, with alternative arrangements of single and double bonds. Mesomerism between different valency structures is accepted therefore in the case of phenanthrene.

The way in which the three six-rings are arranged in the molecule of phenanthrene is called *angular annellation* since the centres of the three hexagons do not lie on a straight line; in anthracene on the other hand, one speaks of *linear annellation* since the centres of the three hexagons now lie on a straight line.

From the structural formula of phenanthrene it follows that five isomeric monosubstitution products are possible, since 1=8, 2=7, 3=6, 4=5 and 9=10.

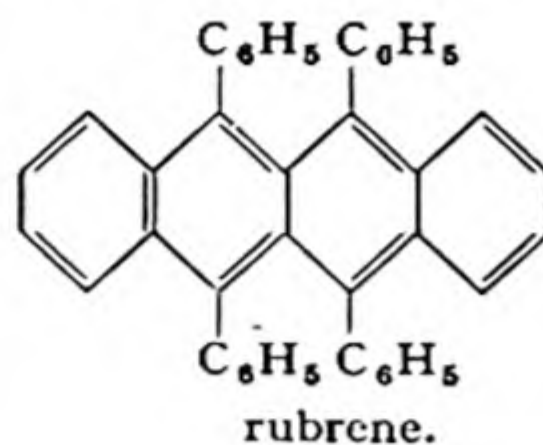
Phenanthrene easily adds on a molecule of bromine, the bromine atoms being attached to carbon atoms 9 and 10. By catalytic hydrogenation with a copper-chromium oxide catalyst, *dihydrophenanthrene* is produced, in which an atom of hydrogen is added to each of carbon atoms 9 and 10. In the above-mentioned oxidation of phenanthrene with chromic acid, the 9 and 10 CH-groups are oxidised to carbonyl groups. The group —CH=CH— is therefore the reactive group in phenanthrene and in this respect is comparable with the CH-groups in positions 9 and 10 in the anthracene molecule.

In both cases these reactive CH-groups make up part of a six-ring which is condensed with two other six-rings.

Phenanthraquinone crystallises in orange coloured needles melting at 205°. It is odourless, non-volatile with steam and can be distilled without decomposition. A dioxime can be produced by the action of hydroxylamine on phenanthraquinone and the latter also forms an addition compound with sodium bisulphite. Hence phenanthraquinone shows the properties of a diketone; on the other hand, it also shows some of the properties of a quinone, as is apparent, for example, in its easy reduction to *phenanthrahydroquinone*, which is very easily reoxidisable.

The phenanthrene ring system occurs in the molecules of a number of important natural products including cholesterol and related compounds

and when exposed to light readily takes up a molecule of gaseous oxygen giving a colourless oxide, which decomposes again into oxygen and rubrene when warmed while being irradiated with light. Thus this is an example of a hydrocarbon, which can form a dissociable oxide (MOUREU and DUFRAISSE):



CHAPTER 10

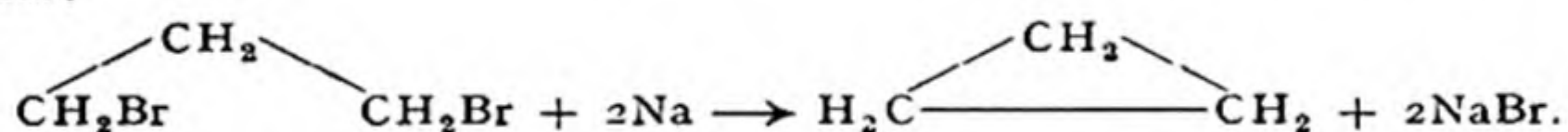
ALICYCLIC COMPOUNDS

(i) CYCLANES AND THEIR DERIVATIVES

286. *Cyclanes* are hydrocarbons having the general formula C_nH_{2n} ; they are isomeric with the alkenes but have a cyclic structure (81). Although they show similarities in chemical behaviour with the aliphatic compounds from whence they derive the name "alicyclic", they possess important differences due to the cyclic structure of the molecule.

First of all, general methods of preparation and properties will be given for cyclanes with 3, 4, 5, 6 or more carbon atoms in the ring, and then some of the most important derivatives of this large group of compounds will be discussed in more detail.

Cyclopropane C_3H_6 , the first member of the homologous series of cyclanes, is prepared by treating 1,3-dibromopropane (108) dissolved in boiling xylene with sodium:



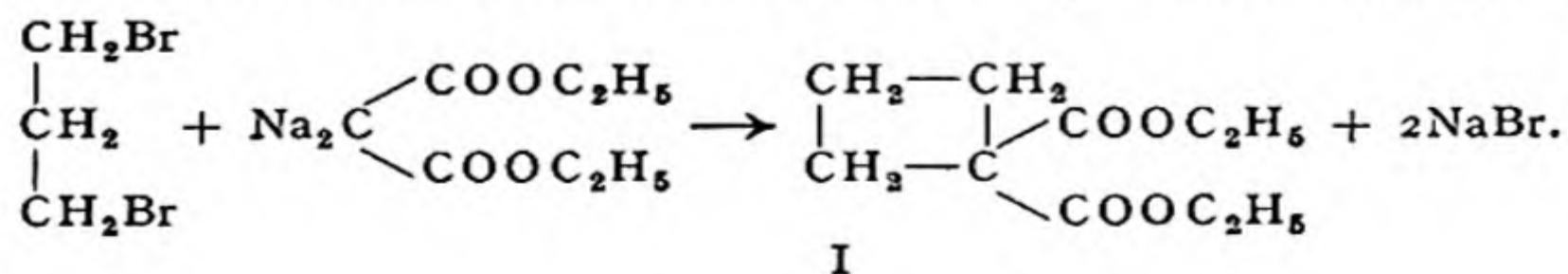
In this reaction, propene (81) is also produced as an isomeric by-product.

Unlike propene, cyclopropane (b.p. -32.9°) does not react with dilute potassium permanganate solution at ordinary temperatures. *n*-Propyl iodide is formed by the action of very concentrated hydriodic acid at 0° . Bromine reacts slowly with the formation of 1,3-dibromopropane. When cyclopropane is passed over aluminium oxide at 250° it is partially converted into propene.

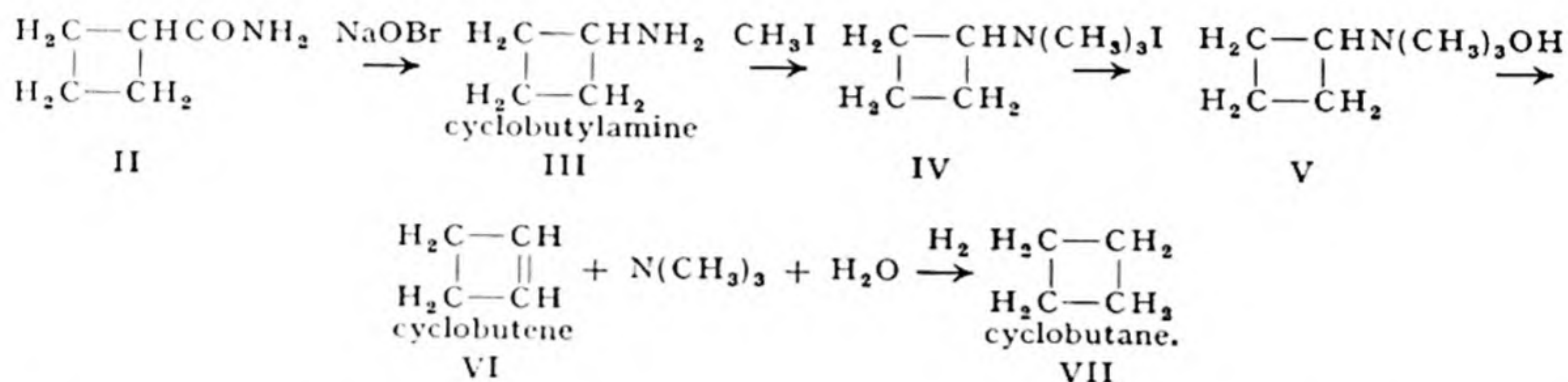
When cyclopropane is mixed with hydrogen and the mixture is passed over finely divided nickel, it is converted into *n*-propane.

In these reactions the ring of three carbon atoms in the cyclopropane molecule readily passes over into an open chain configuration containing three carbon atoms.

Cyclobutane C_4H_8 . Derivatives of this compound can be obtained by the interaction of di-sodium ethyl malonate and 1,3-dibromopropane (PERKIN):

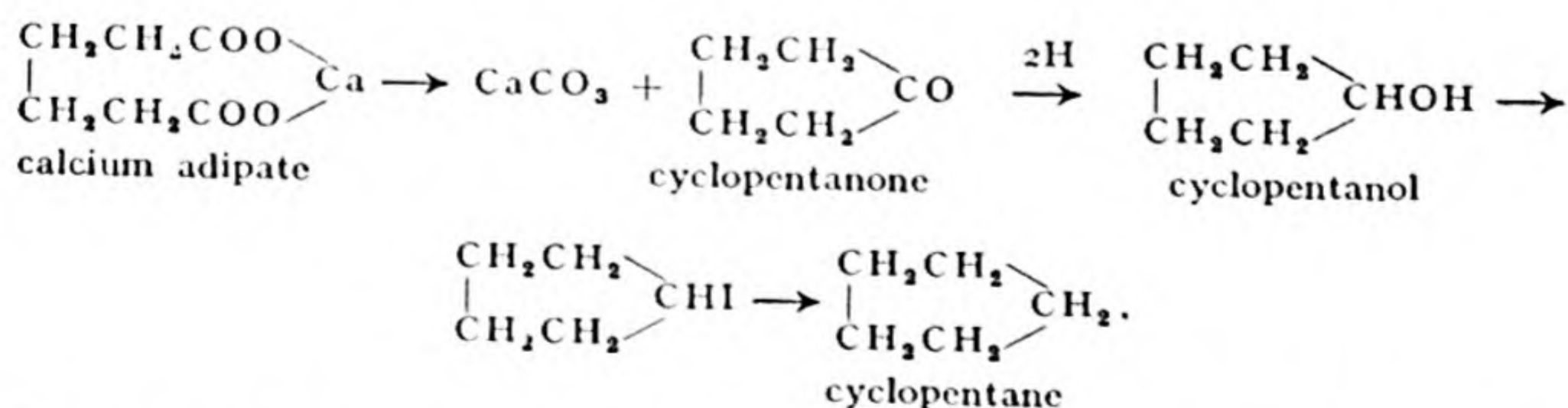


In this reaction diethyl cyclobutane dicarboxylate (I) is produced; cyclobutane dicarboxylic acid, obtained from the ester on hydrolysis, loses carbon dioxide on heating, with the production of cyclobutane mono-carboxylic acid. Cyclobutane was prepared from this acid by WILLSTÄTTER, by a method which can also be applied in other cases for the preparation of hydrocarbons (216). The amide of cyclobutane mono-carboxylic acid (II) is converted into cyclobutylamine (III) (78); by methylating this amine, the quaternary ammonium iodide (IV) is obtained; the quaternary base V is decomposed by heating with the formation of cyclobutene (VI), which is converted into cyclobutane (VII) by catalytic hydrogenation over nickel at 100°:



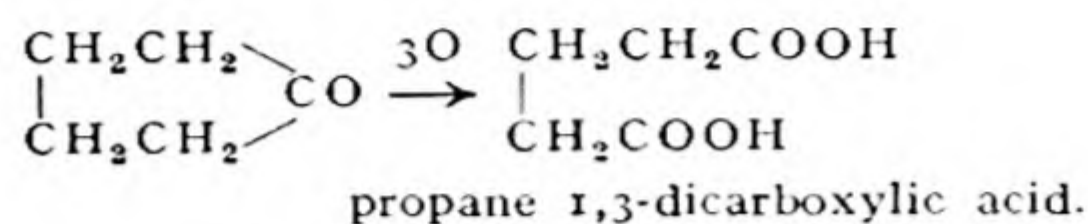
Cyclobutane reacts at 0° with concentrated hydriodic acid. It reacts with hydrogen over finely divided nickel to form *n*-butane but not below a temperature of 180°. From this it follows that the ring of four carbon atoms in cyclobutane is opened less readily than the ring of three carbon atoms in cyclopropane.

287. Cyclopentane C_5H_{10} . Derivatives of cyclopentane and the higher members of the series can be prepared by the following general method. *Alicyclic ketones* are produced by heating the calcium salt of a dibasic acid of the type $\text{HOOC}(\text{CH}_2)_n\text{COOH}$, in which *n* is greater than three. Thus cyclopentanone is produced from calcium adipate, and this can be converted into cyclopentane via the secondary alcohol, cyclopentanol, the iodide iodo-cyclopentane, and reduction of the latter:



The structure of cyclopentane follows from this method of formation and

from the oxidation of cyclopentanone to propane 1,3-dicarboxylic acid (glutaric acid):

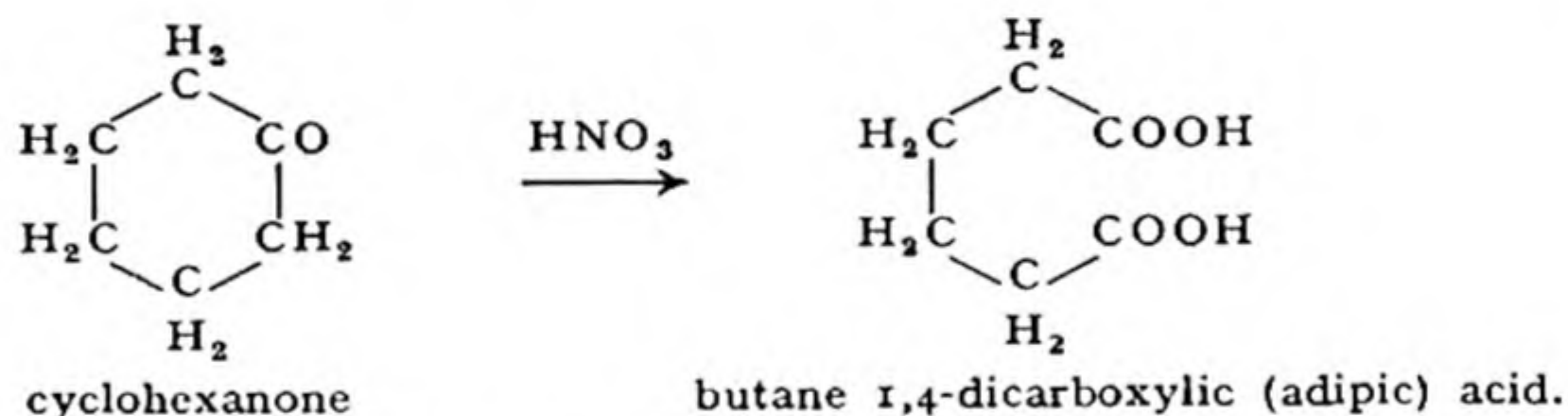


Cyclopentane is also produced by the action of zinc dust on 1,5-dibromopropane.

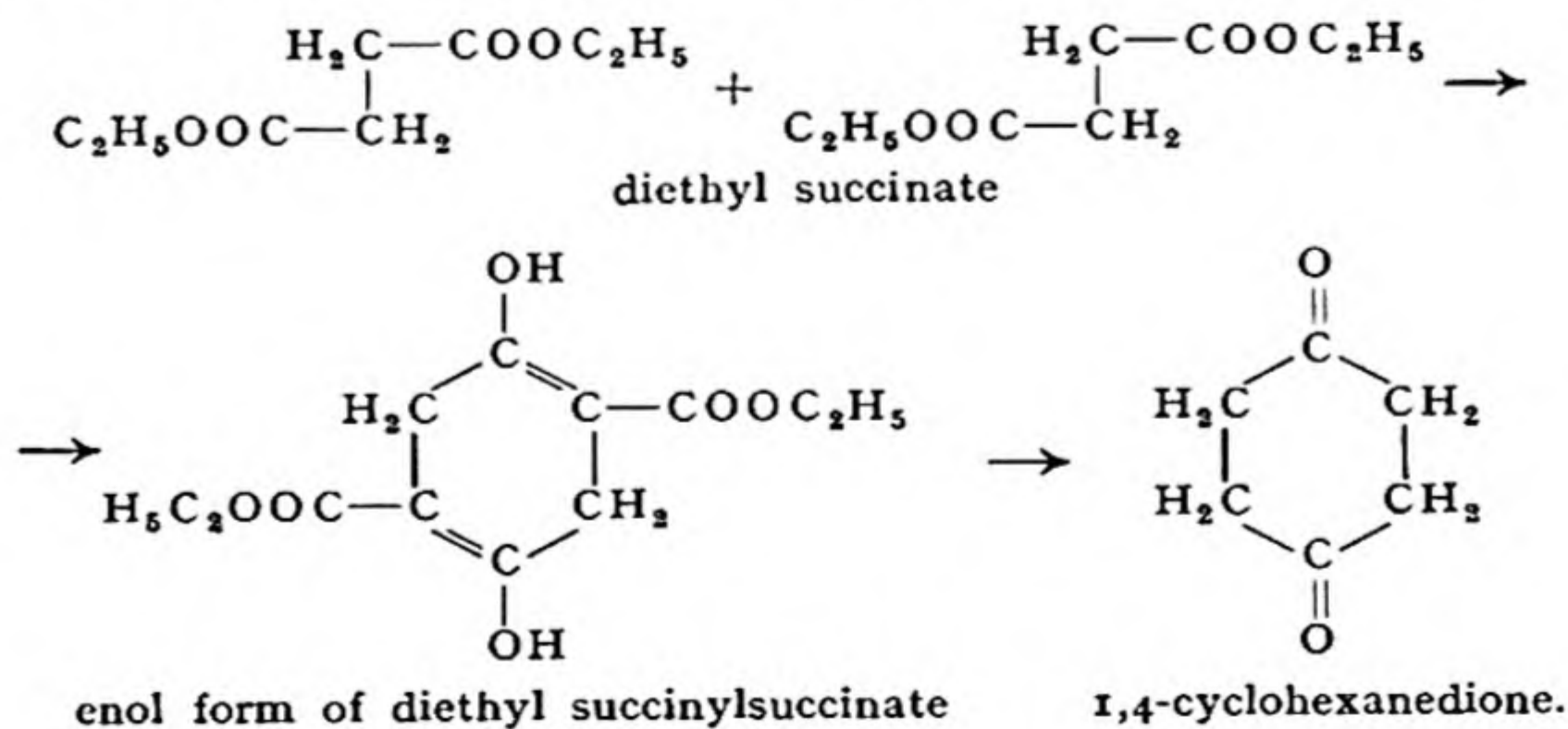
Cyclopentane behaves like a saturated hydrocarbon. It does not react with hydriodic acid below 200° . At ordinary temperatures it is quite stable towards dilute potassium permanganate solution. *n*-Pentane is produced from cyclopentane by catalytic reduction over platinum; for this to occur, however, a temperature of $300\text{--}310^\circ$ is necessary. From these examples it follows that the cyclopentane ring is opened only with difficulty.

Cyclohexane C_6H_{12} . By heating the calcium salt of pentane 1,5-dicarboxylic (pimelic) acid there is formed *cyclohexanone*, from which *cyclohexanol* (289) is produced by reduction; by splitting off water from the latter compound, *cyclohexene* is obtained, which may be reduced catalytically to cyclohexane.

An almost quantitative yield of butane 1,4-dicarboxylic (adipic) acid is obtained by oxidising cyclohexanone. This establishes the structure of this cyclic ketone:



Cyclohexane and its derivatives were first studied by BAEYER (1894) who applied the following elegant synthesis for their preparation: under the influence of sodium ethylate, diethyl succinate undergoes a condensation comparable with the ester condensation of CLAISEN and WISLICHENUS (146):



In this reaction *diethyl succinylsuccinate* is formed, from which the free acid is obtained on hydrolysis; on heating, the acid decomposes into two molecules of carbon dioxide and one of cyclohexan-1,4-dione. The latter can be converted into cyclohexane by reduction; this confirms the cyclic structure of the diketone.

For a tautomeric conversion of a cyclohexane derivative into a benzene derivative see section 215.

Cyclohexane is prepared by the catalytic hydrogenation of benzene (214). Like cyclopentane it behaves like a saturated hydrocarbon. It forms substitution products *e.g.* *mono-chlorocyclohexane* by the action of chlorine. From this it appears that the cyclohexane ring is not easily opened.

Cycloheptane C_7H_{14} is prepared by the general method from calcium suberate (hexane 1,6-dicarboxylate), which is converted via the cyclic ketone and alcohol into cycloheptyl bromide, from which the hydrocarbon is produced by reduction.

In order to prepare the higher ketones with 10 or more carbon atoms in the ring, use is made of the thorium salts of the appropriate dibasic acids, *e.g.* $HOOC(CH_2)_nCOOH$ (for the preparation of these acids see 123). RUZICKA has employed this method to make all the cyclanones containing from ten to thirty carbon atoms in the ring (see 293).

It is a remarkable fact that these compounds are very stable. For example, when cycloheptadecanone $(CH_2)_{14}CO$ is heated to 400° or when it is heated with hydrochloric acid, only a small amount of decomposition occurs. In a number of cases the corresponding cyclanes can be prepared by boiling the cyclic ketones with amalgamated zinc and hydrochloric acid (CLEMENSEN'S method of reduction). The higher cyclanes are again very stable compounds; cyclopentadecane $C_{15}H_{30}$ and cycloheptadecane $C_{17}H_{34}$ are not decomposed by heating with hydriodic acid.

The relationship between the number of carbon atoms in the ring and the properties of the cyclanes

288. When the properties of the cyclanes are compared, it is seen that the three-ring in cyclopropane readily passes into an open chain, the four-ring in cyclobutane does this less readily and the cyclopentane ring is opened only with difficulty. These phenomena are in complete agreement with the strain theory of BAEYER (82). According to the structural formula of cyclopropane the angles between the C—C bonds is 60° . This molecular model is in accordance with the results of electron diffraction measurements on gaseous cyclopropane.

The deviation from the direction of a tetrahedral bond arrangement amounts to $\frac{109^\circ 28' - 60^\circ}{2} = 24^\circ 44'$ per C—C bond for the three ring. The

deviation for the four ring is $\frac{109^{\circ}28' - 90^{\circ}}{2} = 9^{\circ}44'$ and for the five-ring $\frac{109^{\circ}28' - 108^{\circ}}{2} = 0^{\circ}44'$, if it is assumed that the carbon atoms of the four- and five-rings lie in one plane. Thus the "strain" is greatest in the three-ring and there is practically no strain in the five-ring.

When the structure of the cyclanes with more than five carbon atoms are represented by polygons in which the carbon atoms lie in one plane, the deviation for the C—C bond becomes negative; for the six-ring this deviation becomes $\frac{109^{\circ}28' - 120^{\circ}}{2} = -5^{\circ}16'$, for the seven-ring $-9^{\circ}33'$ and for the seventeen-ring $-24^{\circ}41'$. According to BAEYER's strain theory it must be expected that cyclic molecules with a large number of carbon atoms in the ring should be "unstable" *i.e.* should be easily convertible into aliphatic compounds. This latter conclusion is not in accordance with observations. It is, however, possible to construct models for rings of carbon atoms in which the angles between the C—C bonds are $109^{\circ}28'$, if it is assumed that the atoms no longer lie in one plane. SACHSE had already put forward such "strain free" models for cyclohexane in 1890; this theory was elaborated still further by MOHR in 1918. Two strain-free models can be constructed for cyclohexane as shown in the "bed" (I) and "chair" (II) formulae in Figure 65.

Strain-free models in which the carbon atoms do not lie in one plane, can also be constructed for rings with more than six carbon atoms. The stability of the higher cyclanes is in accordance with this idea.

The objection that two isomers ought to exist if a non-planar ring is assumed for cyclohexane, no longer holds if at the same time it is assumed that the two spatial configurations are readily convertible one into the other. This idea is supported by investigations on the stereochemical configuration of the cyclane-1,2-diols (BOESEKEN 1921).

For the preparation of cyclopentane-1,2-diol the starting material is cyclopentanol, from which cyclopentene is produced by the removal of a molecule of water and this compound is then converted into the diol by the action of dilute potassium permanganate solution:

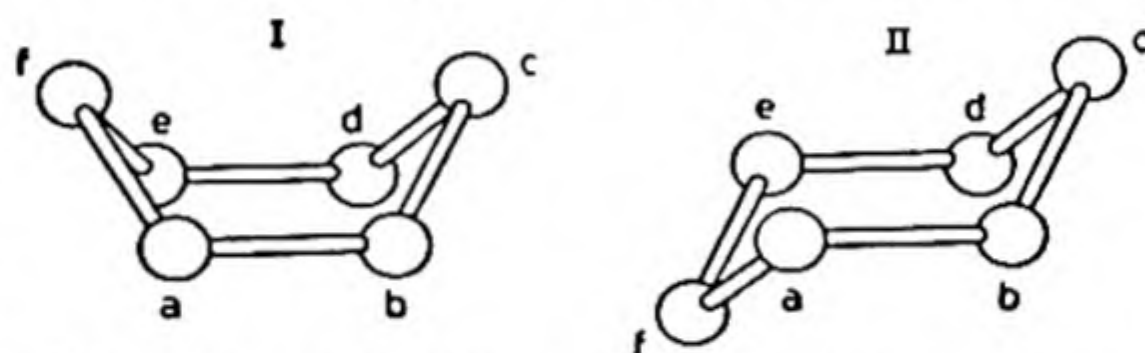
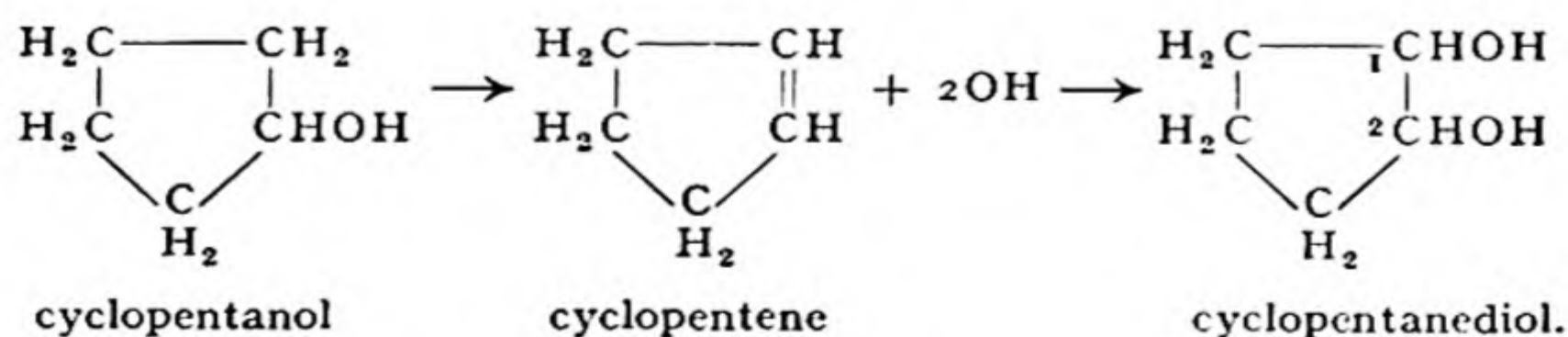


Fig. 65. "Bed" and "chair" formulae for cyclohexane.

This diol, which melts at 30.5° , reacts with acetone in the presence of condensing agents; the formation of such isopropylidene derivatives is characteristic of dihydric alcohols in which the two hydroxyl groups occupy a favourable position, therefore the *cis*-configuration is assigned to this cyclopentane-1,2-diol. This is in agreement with the further observation that it increases the conductivity of boric acid solutions.

The molecule of cyclopentanediol contains two identical asymmetric carbon atoms 1 and 2 (compare 134). From the model it is apparent that the *cis*-form has a plane of symmetry and cannot therefore occur in mirror-image forms. The *trans*-form, however, can occur in two mirror-image forms (see Fig. 66):

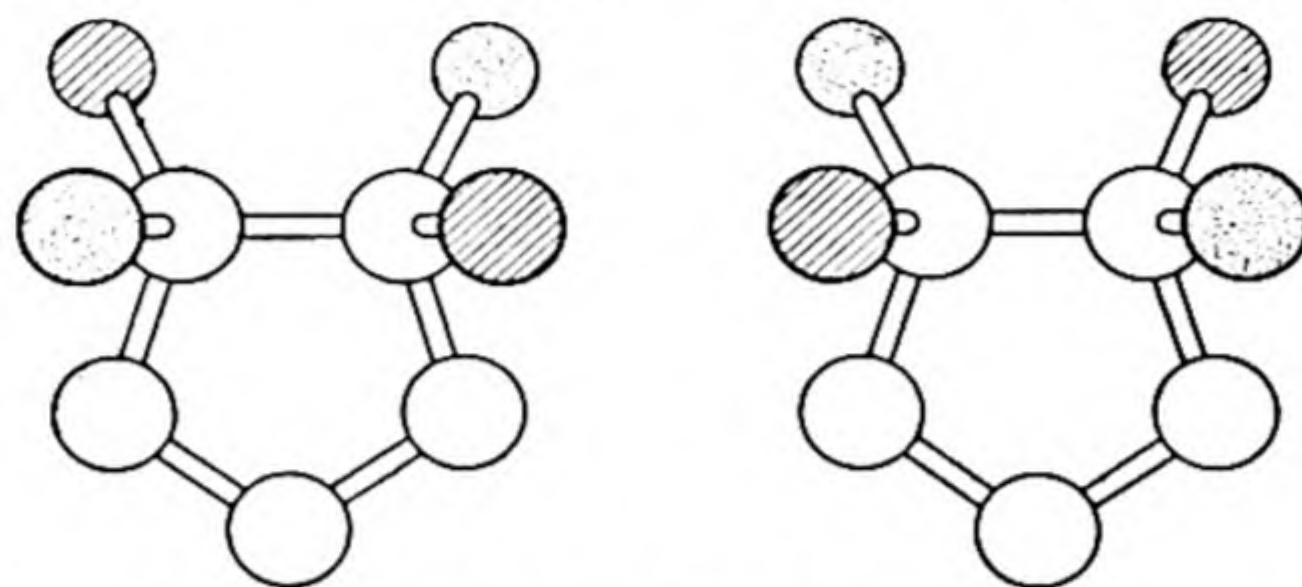
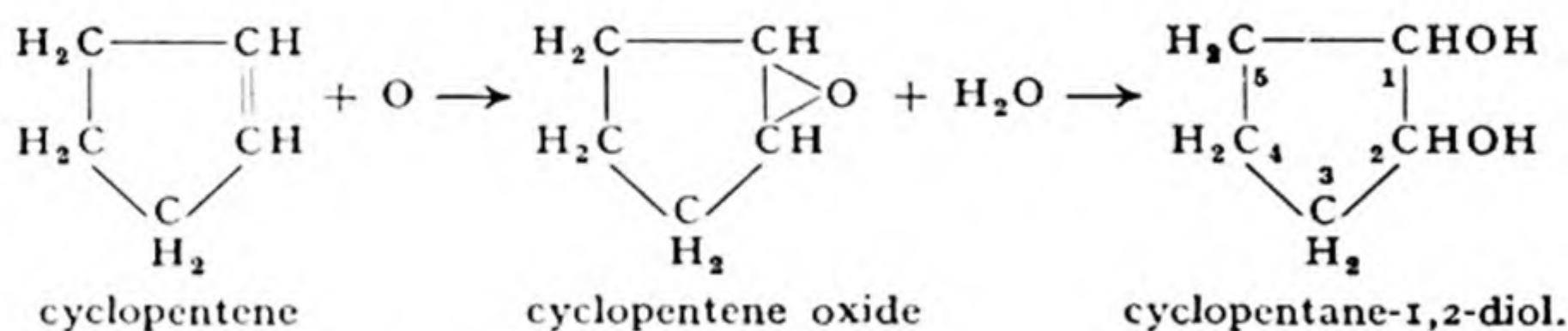


Fig. 66. *trans*-Cyclopentanediol, two mirror-image forms.

A cyclopentane-1,2-diol melting at $54-55^\circ$, is produced by treating cyclopentene with perbenzoic acid (260) and heating the resultant cyclopentene oxide with water:



This diol is a mixture of optical antipodes. This is shown by the formation, by the action of menthyl isocyanate, of two different urethanes (152), in which the menthyl group (294) is asymmetric. Hence this diol has the *trans*-structure. As is to be expected it does not react with acetone, because the hydroxyl groups are situated in the *trans*-position and it does not increase the conductivity of boric acid solutions.

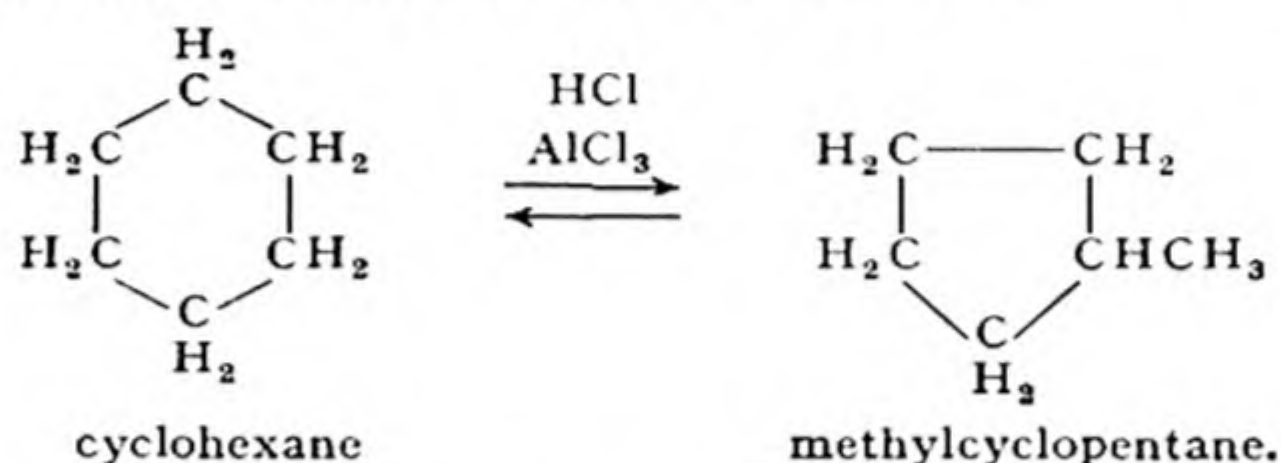
In a similar way two stereoisomeric 1,2-diols (*cis*- and *trans*-forms) have been obtained from cycloheptene. Both forms, however, react with acetone and increase the conducting power of boric acid. This result would be inexplicable if the cycloheptane ring had a flat structure; in accordance with the idea of the strain-free model, this ring can take up different spatial configurations, in which those configurations in which the hydroxyl groups are situated in a favourable position, occur with sufficient frequency in both the *cis*- and *trans*-forms, to exert a positive influence on the conducting powers of boric acid and on the ability to react with acetone.

Physical properties of the cyclanes. The molecular heat of combustion is approximately additive from cyclopentane onwards, *i.e.* the increase in the molecular heat of combustion from the five-ring to the six-ring and from the six-ring to the seven-ring, etc., is approximately the same. This is in agreement with the assumption that there is no strain in these rings. The heat of combustion of cyclopropane is greater than

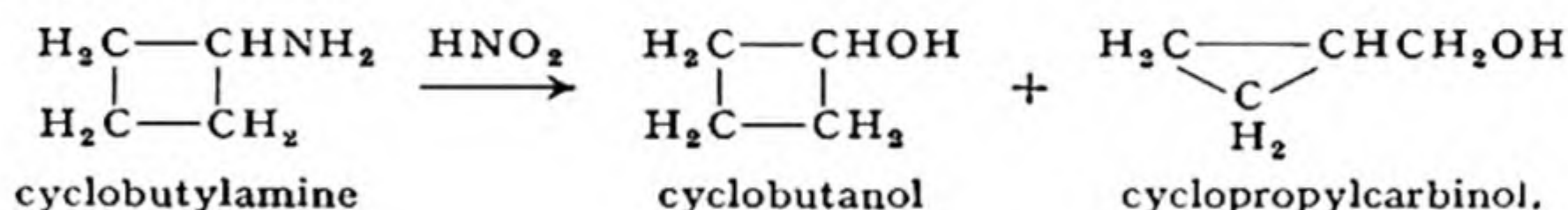
the value agreeing with three times the value for the CH_2 -group, which indicates the existence of strain in this ring. The energy, which has been necessary to bind the CH_2 -groups in a three-ring is liberated on combustion and therefore the heat of combustion is greater than would be expected for three CH_2 -groups.

The boiling points are higher than those of the corresponding isomeric alkenes (compare Table 50); the specific gravity of a cycloalkane is about 0.1 higher than that of the isomeric alkene. When the molecular refractions of the cyclanes are compared, as the number of carbon atoms in the ring increases, it is found that from cyclopentane onwards the increase per cyclically combined CH_2 -group amounts to about 4.6. This is the same increment per CH_2 -group as is found in the alkane series (see 23).

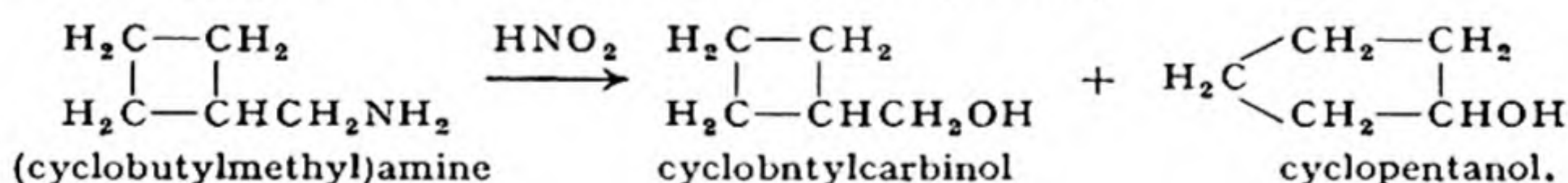
Alteration in the ring-system. The cyclanes can undergo reactions in which both "expansion" and "contraction" of the ring may occur. By boiling with aluminium chloride and some hydrogen chloride cyclohexane may be converted into *methylcyclopentane* (NENITZESCU). This reaction is reversible:



By the action of nitrous acid on cyclobutylamine, *cyclopropylcarbinol* is produced as well as cyclobutanol:



When nitrous acid is allowed to react with cyclobutylmethylamine, *cyclobutylcarbinol* and cyclopentanol are produced (DEMJANOW):



Some derivatives of the cyclanes

289. Cyclopentane, methylcyclopentane, cyclohexane and methylcyclohexane occur in petroleum from the Caucasus and Galicia. In the technical literature these cyclanes are frequently called *naphthenes*.

Derivatives of cyclopentane. In Russian and Galician petroleum there are small quantities of *naphthenic acids*, which have been identified as cyclopentane derivatives:

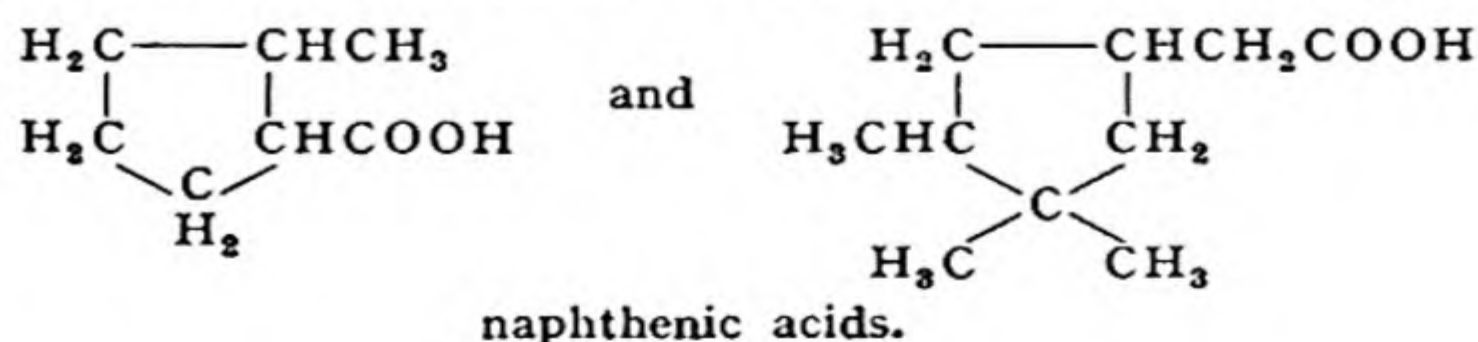
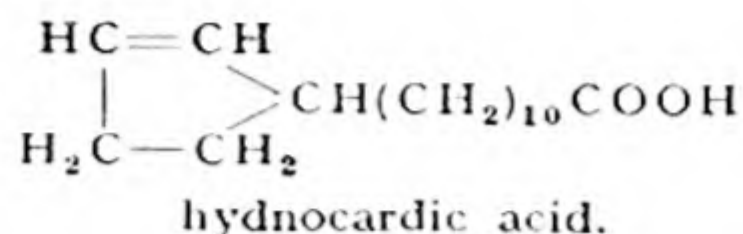
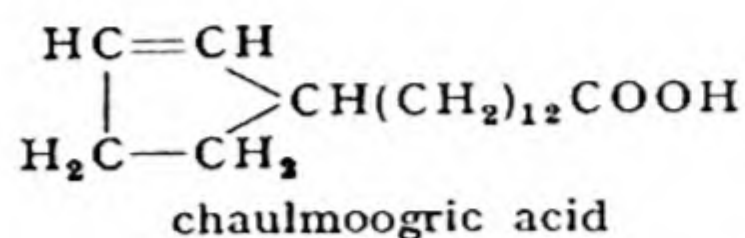


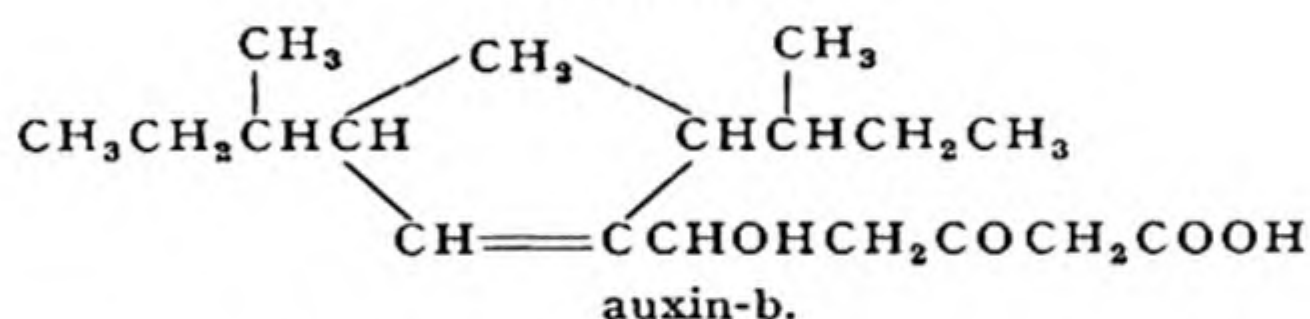
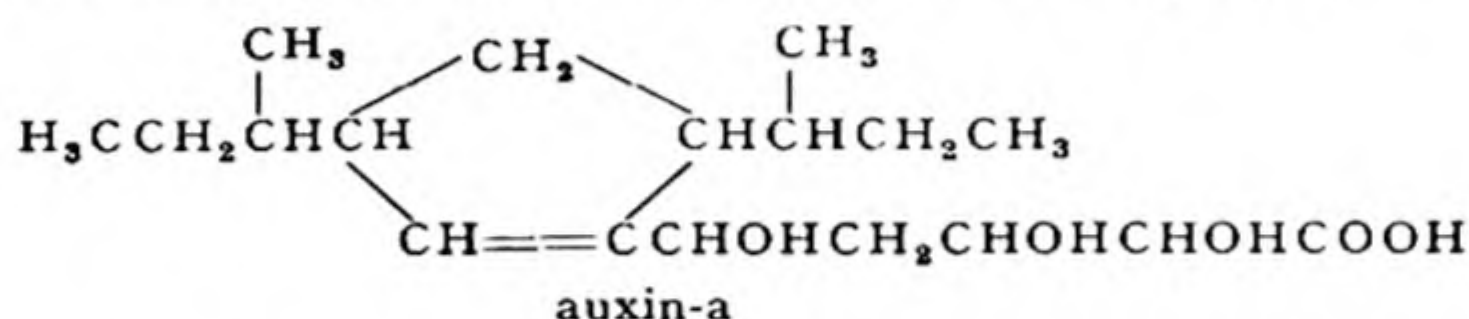
TABLE 50
SOME PHYSICAL CONSTANTS OF CYCLANES

Number of Carbons in Ring	Name	Boiling Point	Melting Point	Density		Refractive Index		Molecular refraction			Mol. heat of combustion at constant volume	Heat of com- bustion per CH ₂ group
				d_4^t	t	n_D^t	t	M_D	t	per CH ₂ group		
3	Cyclopropane	-33°	-127°.56	0.689	-40°	1.377	-40°	14.05	-40°	4.68	506	169
4	Cyclobutane	+12°	-80°	0.7038	0°	1.3752	0°	18.25	0°	4.56	—	—
5	Cyclopentane	49°.3	-94°.4	0.7454	20°	1.4065	20°	23.12	20°	4.63	785	157
6	Cyclohexane	80°.8	6°.4	0.7787	20°	1.4262	20°	27.69	20°	4.62	938	156
7	Cycloheptane	117°	-12°	0.8100	20°	1.4436	20°	32.17	20°	4.60	1089	156
8	Cyclooctane	145°-146°	14°	0.8304	20°	1.4563	20°	36.75	20°	4.59	1253	157
9	Cyclononane	170°-172°	—	0.7733	16°	1.4328	16°	42.47	16°	4.72	—	—
10	Cyclodecane	75°/12 mm.; 201°/760 mm.	9°.5	0.8580	20°	1.4715	20°	45.74	20°	4.57	1576	158
11	Cyclo-undecane	183°.5-184°.5 764.5 mm.	—	0.8128	20°	1.4483	20°	50.84	20°	4.62	—	—
12	Cyclododecane	118°/18 mm.	61°	0.8223	75°	—	—	—	—	—	—	—
13	Cyclotridecane	112°-113°/9 mm.	18°	0.861	20°	—	—	—	—	—	—	—
14	Cyclotetradecane	143°/16 mm.	53°	0.8259	79°	1.4515	80°	64.13	80°	4.58	—	—
15	Cyclopentadecane	—	61°	0.8240	78°	1.4522	80°	69.04	80°	4.60	2344	156
16	Cyclohexadecane	170°-171°/20 mm.	57°	0.819	79°	1.4529	80°	74.12	80°	4.63	—	—
17	Cycloheptadecane	—	65°	0.8200	77°	1.4507	80°	78.48	80°	4.62	2661	156
18	Cyclooctadecane	—	72°	0.8201	76°	1.4506	80°	83.15	80°	4.62	—	—
22	Cyclodocosane	212°/16 mm.	46°	0.8174	75°	1.4481	80°	101.6	80°	4.62	—	—
23	Cyclotricosane	177°/0.4 mm.	56°	0.8280	60°	1.4558	56°	105.5	56°	4.59	—	—
24	Cyclotetracosane	222°-228°/0.6 mm.	47°	—	—	—	—	—	—	—	—	—
26	Cyclohexacosane	218°-219°/0.5 mm.	42°	0.8120	78°	1.4484	80°	120.5	80°	4.64	—	—
28	Cyclooctacosane	213°-214°/0.25 mm.	48°	0.8103	80°	1.4489	80°	129.7	80°	4.63	—	—
29	Cyclononacosane	—	47°	0.8232	64°	—	—	—	—	—	—	—
30	Cyclotriacontane	230°/0.2 mm.	56°	0.8180	77°	1.4523	80°	130.3	80°	4.64	4650	155

Chaulmoogric acid (m.p. 68°) which occurs in chaulmoogra-oil (from the seeds of *Hydnocarpus* species) and *hydnocarpic acid* are unsaturated acids in which a cyclopentene ring is present. Both acids are used as drugs against leprosy:

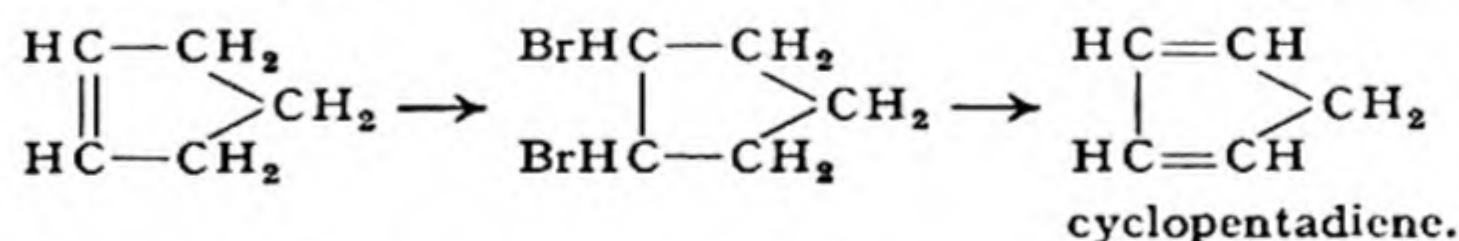


The vegetable growth substance, *auxin* $\text{C}_{18}\text{H}_{30}\text{O}_4$, which promotes the swelling of the cells in oat seedlings, is a biologically important cyclopentene derivative. KÖGL has isolated two auxins. *Auxin-a* occurs in oat seedlings and also in urine. The closely related *auxin-b* has so far been obtained only from maize-germ oil and malt. The quantities of auxins present in the sources mentioned, are extremely small. The structures of these substances have been established by KÖGL:



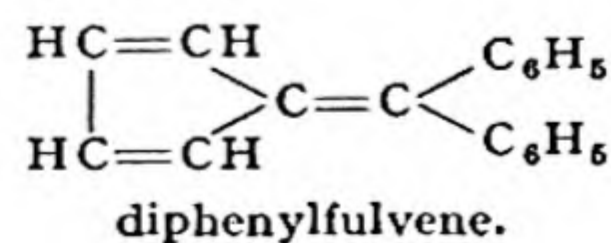
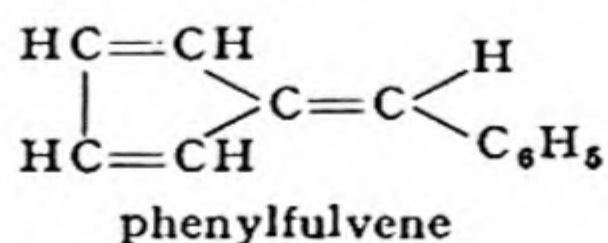
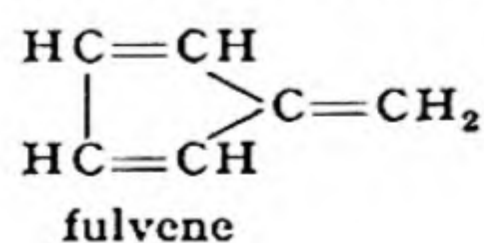
Auxin-a easily forms a lactone, which is converted into a physiologically inactive compound, "lumi-auxone", under the influence of ultraviolet light.

Cyclopentadiene, which is obtained from the forerunnings in the distillation of coal-tar, may be obtained synthetically by adding a molecule of bromine to cyclopentene and removing two molecules of hydrogen bromide from the resultant dibromide by heating with sodium acetate. The structure follows from this synthesis:



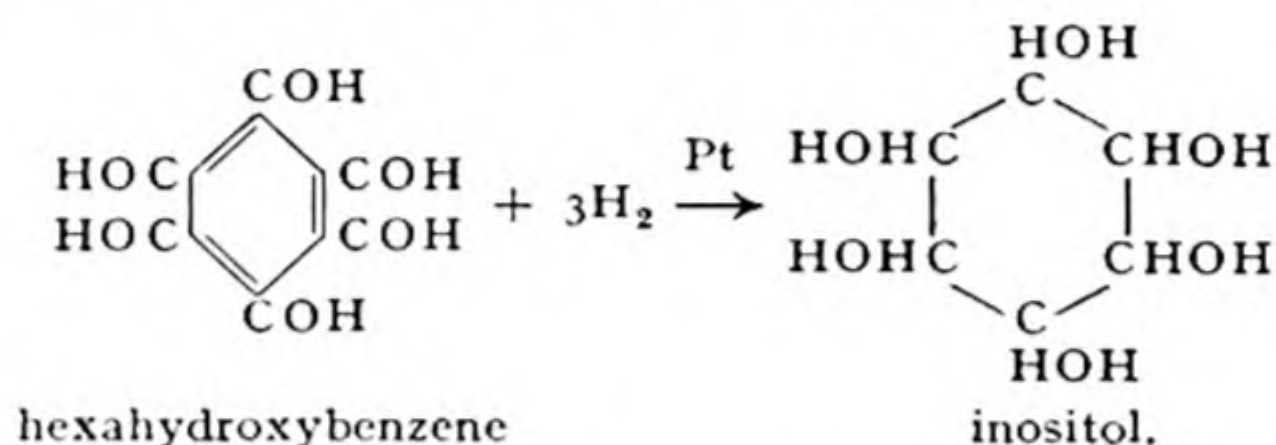
Cyclopentadiene, which boils at 47° , readily polymerises to *dicyclopentadiene* $\text{C}_{10}\text{H}_{12}$; this can be converted into the monomeric form by heating. The hydrogen atoms on the CH_2 -group in cyclopentadiene are very reactive; with aldehydes and ketones, *e.g.* benzaldehyde and benzophenone, condensation products are produced with the elimination of water; they are strongly coloured and are therefore called *fulvenes* (THIELE).

The simplest compound of this group, *fulvene*, C_6H_6 which is obtained from formaldehyde and cyclopentadiene, is yellow in colour; it is very unstable. The phenyl-derivatives are red and are more stable:

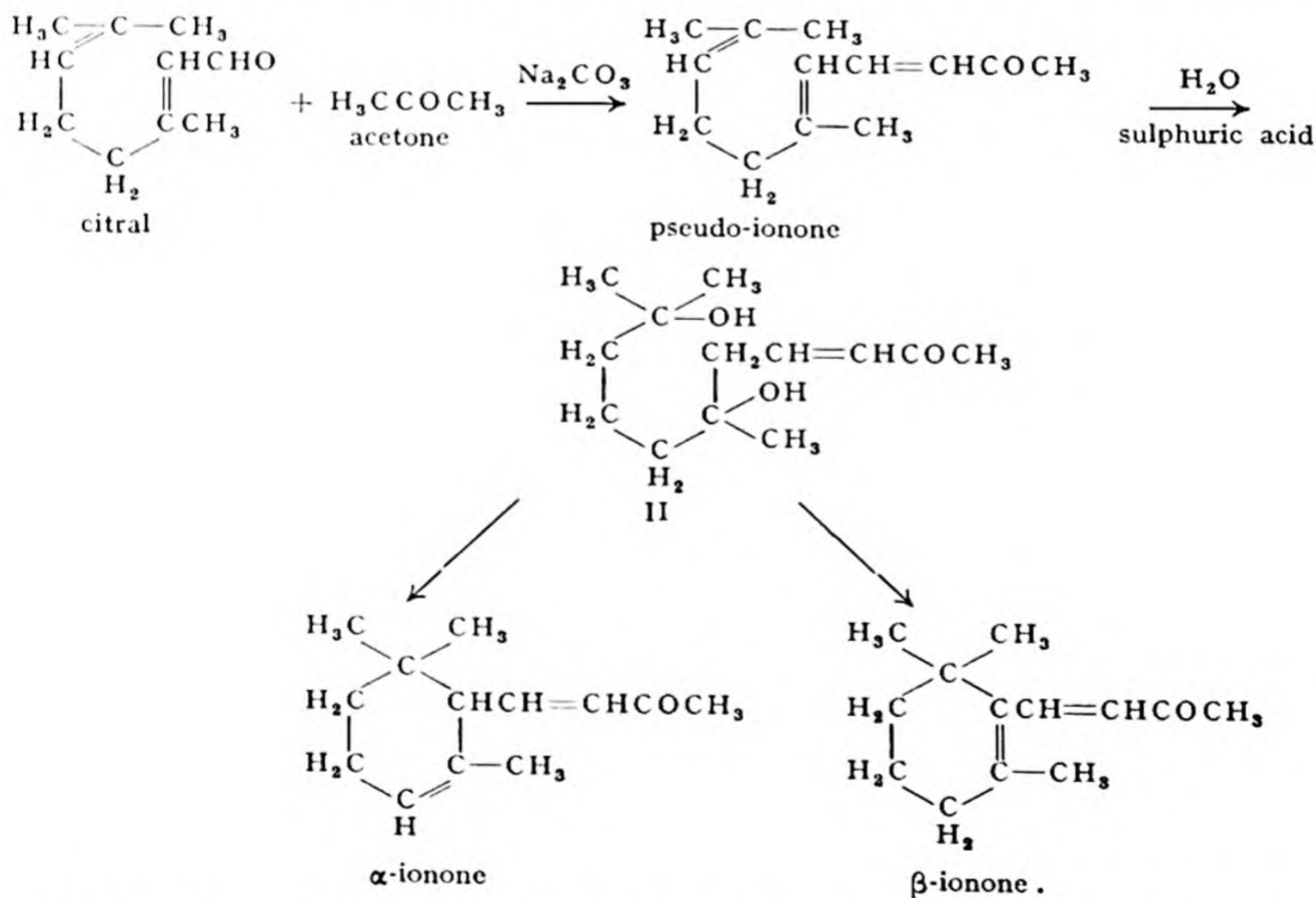


Derivatives of cyclohexane. Cyclohexanol $C_6H_{11}OH$ (b.p. 161.5° , m.p. 23.5°) is prepared on a technical scale by the catalytic hydrogenation of phenol (229) and has the properties of a secondary alcohol. It is used as a solvent for cellulose esters and phenolic resins.

Hexahydroxycyclohexane or inositol, $C_6H_{12}O_6$, which occurs in many plants, *e.g.* in leguminosae, and in animal organs such as the liver, heart muscle and brain, is a hexahydric alcohol derivative of cyclohexane. Inositol has a sweet taste. It can be converted into a hexa-acetate, from which it follows that six hydroxyl groups are present. It can be obtained by the catalytic hydrogenation of hexahydroxybenzene, a reaction which proves the structure of this compound:



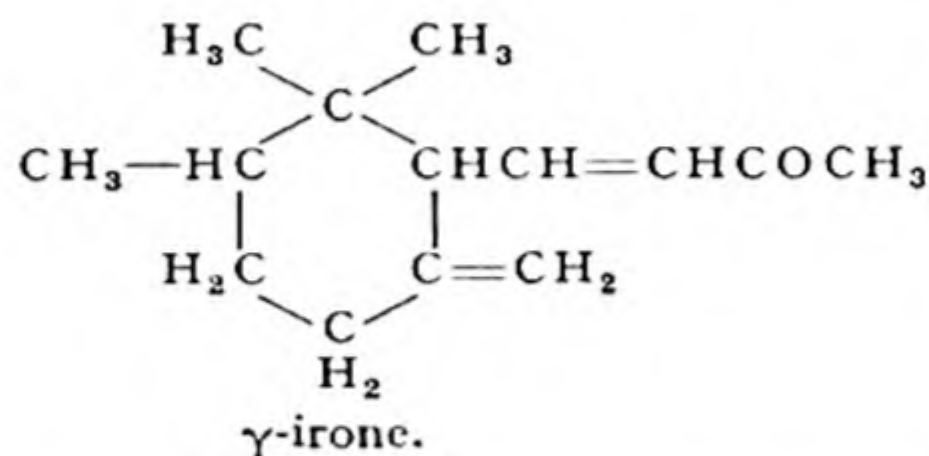
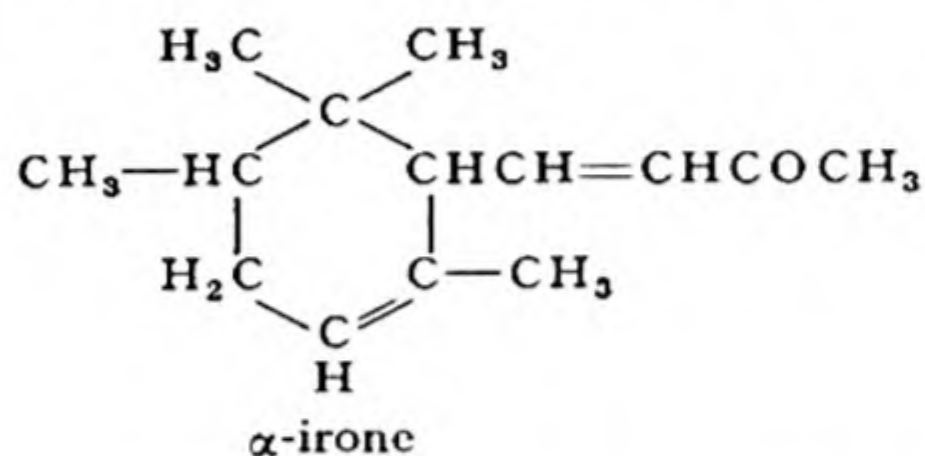
290. Ionone $C_{13}H_{20}O$ is a synthetic perfume prepared by TIEMANN and KRÜGER. By condensing citral (97) with acetone in a weakly alkaline medium, "pseudoionone" is produced. When this compound is treated with sulphuric acid, ring-closure occurs (probably via the product II) with the formation of a mixture of α - and β -ionone:



The structure of these compounds was established by examining the products obtained from them by oxidation with potassium permanganate. In a very dilute state

α - and β -ionone have the scent of violets; the mixture is used as a perfume. It is noteworthy that the β -ionone ring and the α -ionone ring occur in the molecules of some of the carotenes (see 308).

In the roots of the common iris (*iris florentina*) there occurs a small quantity of a compound, *irone*, which smells like violets. TIEMANN first isolated this substance and assigned to it the composition $C_{13}H_{20}O$. He put forward a structural formula which led to the synthesis of α - and β -ionone just mentioned, substances which should differ from irone according to TIEMANN only in the positions of the double bonds. Later on, RUZICKA found that irone from *iris florentina* is a ketone of the composition $C_{14}H_{22}O$. Irone contains one more methyl group than the ionones. RUZICKA also found that there are two irones (α - and γ - respectively) both of which are constituents of natural irone. The structure of α - and γ -irone has been established by degradation reactions and confirmed by synthesis.:

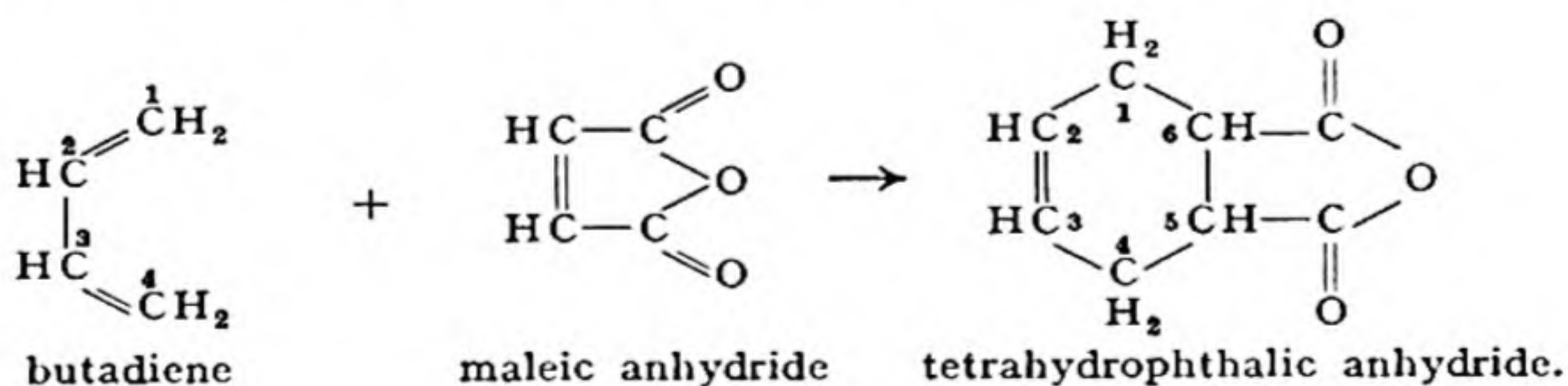


The different kinds of camphor and the terpenes, which occur in the vegetable kingdom in great variety, are also derivatives of cyclohexane. These compounds are discussed in section 294.

Diene-syntheses

291. Derivatives of cyclohexane can be obtained by the general *diene-synthesis* method of DIELS and ALDER.

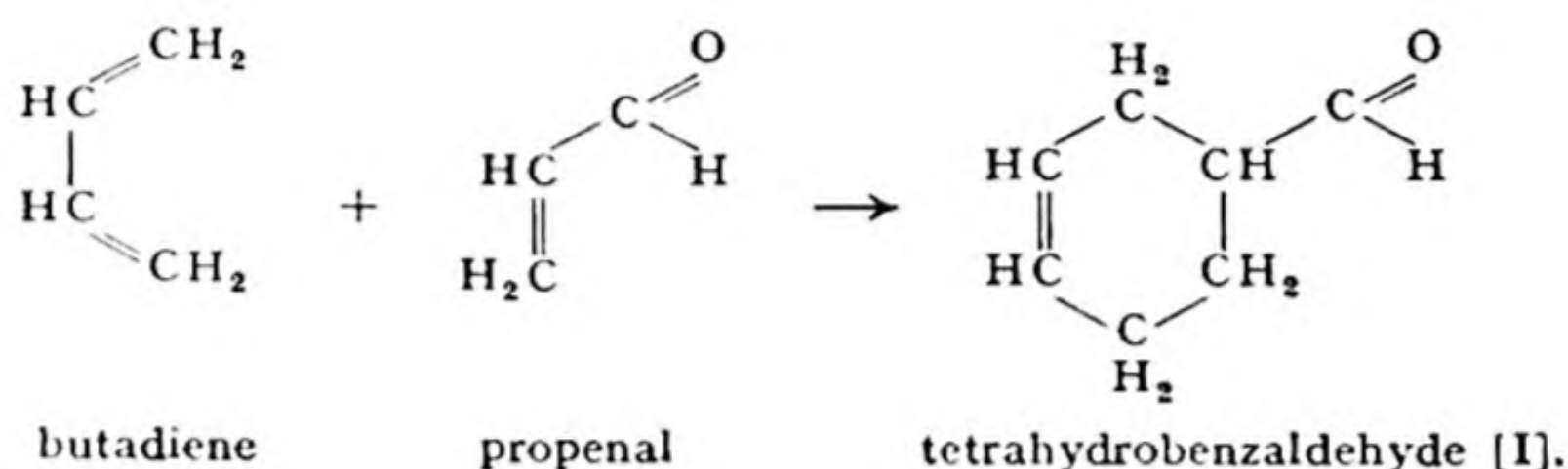
Maleic anhydride (126) adds on very easily to hydrocarbons in which a conjugated system of double bonds is present, *e.g.* with butadiene (92) in benzene solution at 100° , the reaction takes place as follows:



Carbon atoms 1 and 4 in butadiene react and a double bond is produced between carbon atoms 2 and 3 (THIELE'S 1-4 addition 92). Carbon atoms 5 and 6 in the tetrahydrophthalic anhydride are derived from the $C=C$ bond of the maleic anhydride; the high reactivity of this particular bond is ascribed to the $C=O$ bonds with which it is conjugated.

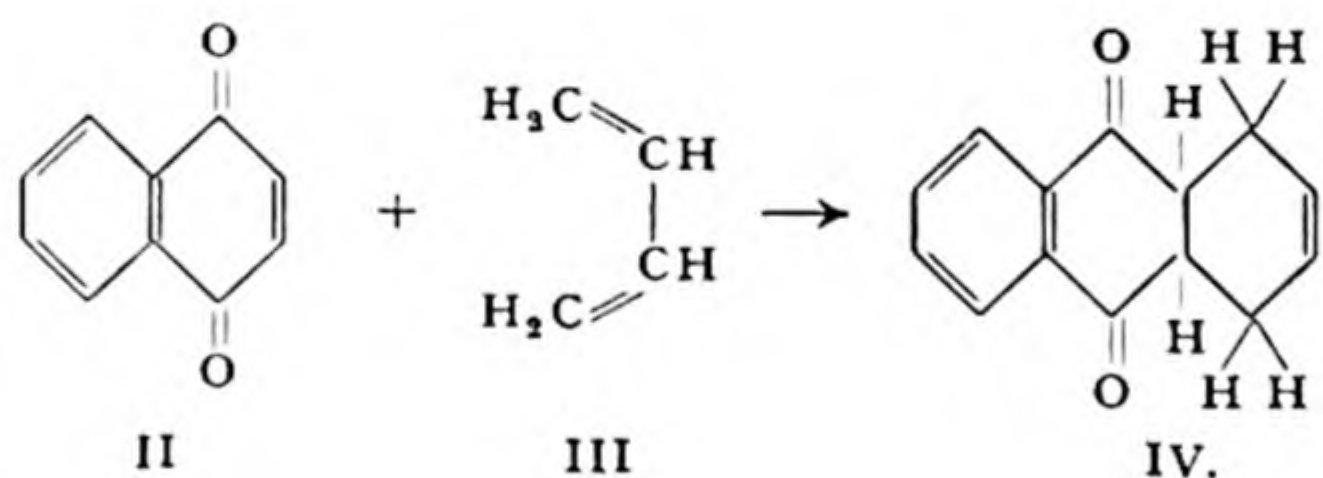
The structure of the addition product follows from its catalytic hydrogenation in alkaline solution (sodium carbonate), to the sodium salt of hexahydrophthalic acid, the anhydride ring being hydrolysed in the process. This same hexahydrophthalic acid can also be obtained by hydrogenating phthalic acid.

The DIELS-ALDER addition also takes place with other compounds besides maleic anhydride in which there is a C=O bond conjugated with a C=C bond (*dienophylic component*). Thus tetrahydrobenzaldehyde is produced from butadiene and propenal:



The semicarbazone of I gives the semicarbazone of hexahydrobenzaldehyde on catalytic reduction; this establishes the structure of I.

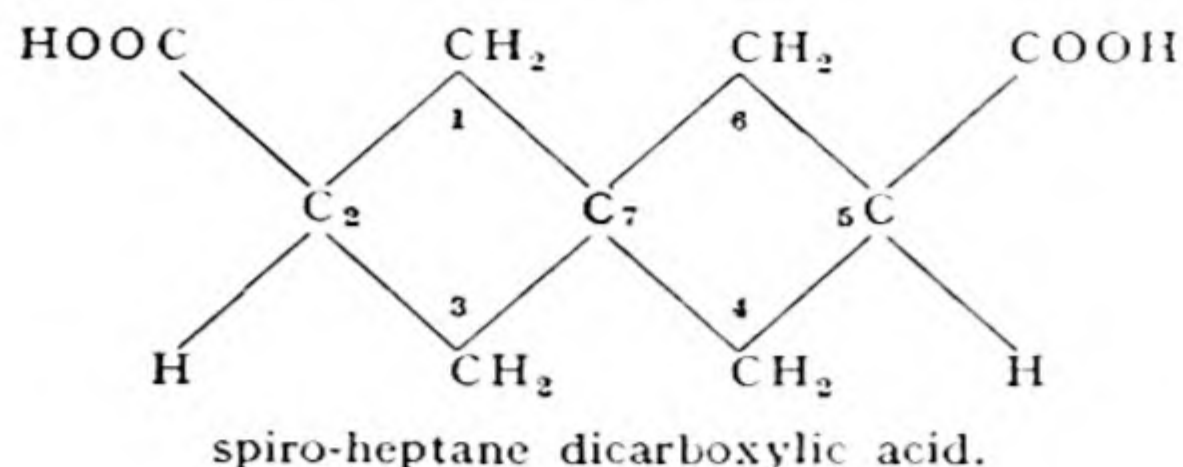
From 1,4-naphthoquinone (II) and butadiene (III), a tetrahydroanthraquinone (IV) is produced, which can be converted into anthraquinone by oxidation with chromic acid:



The diene synthesis can be carried out with various 1,4-dienes such as isoprene, cyclopentadiene, 1,3-cyclohexadiene, etc. Naturally, in the same way, various dienophylic components may be chosen.

Spiranes

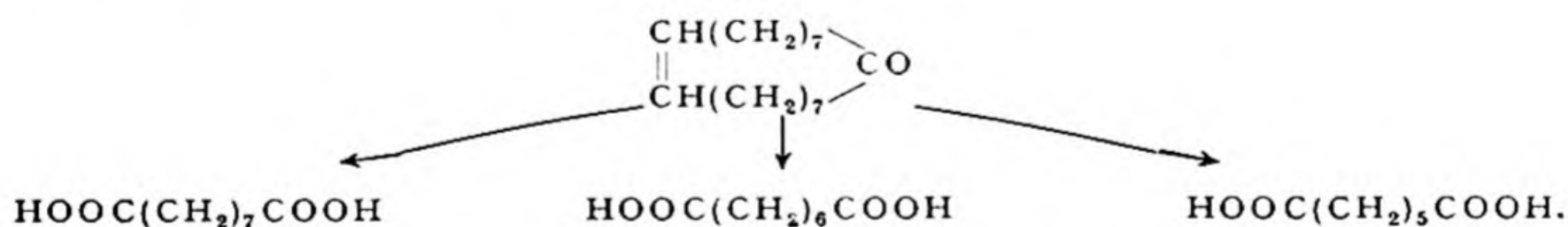
292. In spirocyclic ring-systems there is present a tetravalent atom which forms part of two rings lying in different planes. Compounds containing such a ring system are known as *spiranes* (spira = cracknel). An example is *spiro*-[3,3]-*heptane dicarboxylic acid* (the figures [3,3] in square brackets, indicate that two groups of three atoms forming part of a ring, are joined together through the atom common to both rings) or *spiradicyclobutane dicarboxylic acid*:



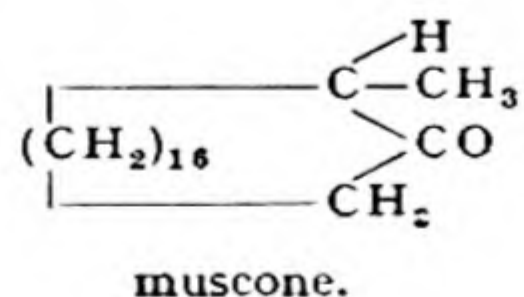
This molecule contains neither a centre nor a plane of symmetry, so that two mirror-image forms are possible (37). The *dl*-form can be resolved by means of the brucine salt, whereby the dextro-rotatory form of spiro-heptane dicarboxylic acid is isolated (BACKER and SCHURINK). For a spirocyclic nitrogen compound see (332). The complex metal compounds of acetylacetone mentioned in 146 and the complex boron compound of salicylic acid mentioned in 263 also have a spirocyclic structure.

Cyclic ketones with a large number of atoms in the ring

293. Two compounds of this group occur in natural products. RUZICKA isolated from *civet*, (a secretory product of the civet cat) an unsaturated cyclic ketone $C_{17}H_{30}O$, *civetone* or *cycloheptadecenone*, having a musk-like odour. By the reduction of civetone, cycloheptadecanone is produced, which is also formed by heating the thorium salt of hexadecane 1,16-dicarboxylic acid, $HOOC(CH_2)_{16}COOH$. Oxidation of civetone with a solution of potassium permanganate gives heptane 1,7-dicarboxylic acid, pentane 1,5-dicarboxylic acid and hexane 1,6-dicarboxylic acid. From these facts the structure of cycloheptadecenone follows:



Muscone, is the odiferous principle of animal musk:



Cyclic ketones with 10-12 carbon atoms in the ring have a camphoraceous odour, while those with 14-18 carbon atoms in the ring have an odour like musk.

(ii) TERPENES AND CAMPHORS

(a) *Terpenes*

294. The *terpenes* form the most important constituents of *essential oils*; they are volatile substances occurring in flowers, leaves and roots of many kinds of plants and in wood, *e.g.* in the resin sap of pine trees, in sandal wood and in camphor wood. Essential oils, which are recovered from the vegetable material by distillation with steam or by extraction with solvents, are always mixtures of various compounds; these are usually liquids but they may also be solid substances like camphor.

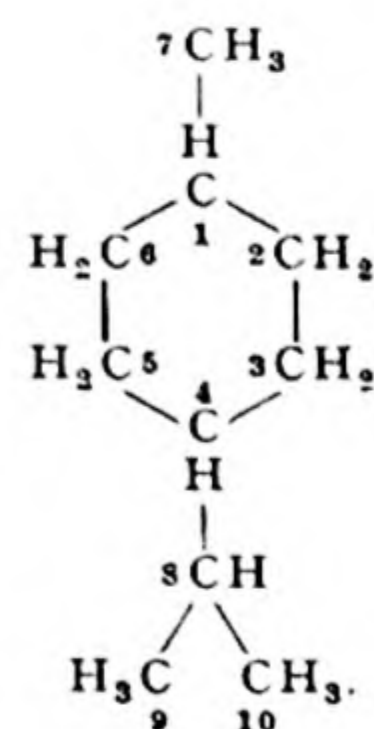
Many terpenes are unsaturated in character and give crystalline addition compounds with hydrogen halides, bromine, nitrosyl chloride and nitrogen trioxide. Use is made of these addition compounds to separate the terpenes from their naturally occurring mixtures; in many cases the terpenes can be recovered in a pure state from these addition compounds. After these methods of isolation had been worked out by W. TILDEN and O. WALLACH, the structure of many of the compounds of this group were elucidated, *e.g.* by BAEYER, GOLDSCHMIDT, PERKIN and WAGNER.

Many of the terpenes and camphors are of practical importance either as perfumes, pharmaceutical products or for industrial purposes. As a rule, some aliphatic compounds, which occur in essential oils, are also classified along with the terpenes. Examples of such compounds are geraniol $C_{10}H_{18}O$, citronellal $C_{10}H_{18}O$ and citral $C_{10}H_{16}O$ (see 97). Only terpenes having a cyclic structure will be discussed in this section.

Monocyclic terpenes

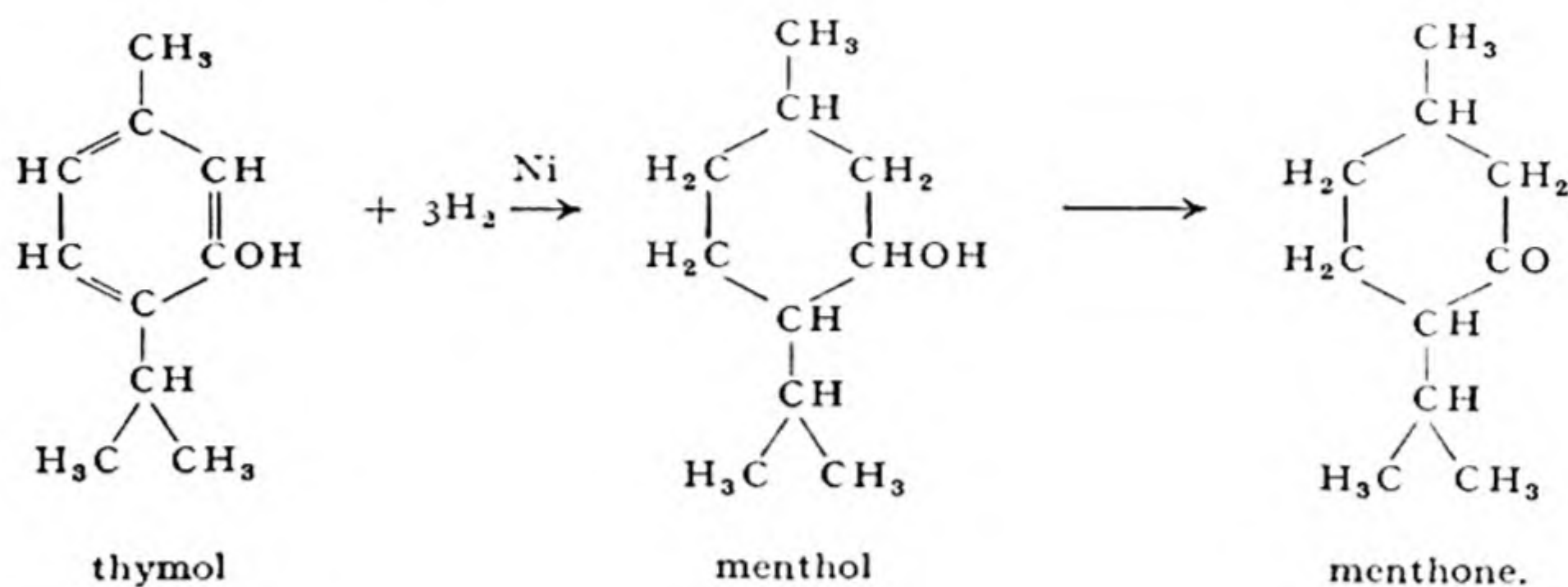
These are derivatives of *menthane* or *hexahydrocymene* $C_{10}H_{20}$. The nomenclature of these compounds is based on the numbering of the carbon atoms given in the annexed formula.

Menthane itself does not occur naturally but can be prepared by catalytic hydrogenation of cymene, in which case either the *cis*-form (b.p. 168.5°) or the *trans*-form (b.p. 161°) is produced as the main product according to whether the reaction is carried out with colloidal platinum or nickel.



295. *l*-Menthane-3-ol or *l*-menthol $C_{10}H_{19}OH$, a monohydric alcohol, occurs in peppermint oils obtained from various kinds of *mentha piperita*. It melts at 43° and boils at 216° ; it is optically active, $[\alpha]_D = -49.4^\circ$, and has an odour like peppermint. On oxidising menthol with chromic acid, a ketone, $C_{10}H_{18}O$, *menthanone* or *menthone*, is produced, hence menthol is a secondary alcohol.

In the catalytic hydrogenation of thymol, *dl*-menthol, which can be resolved into its optical components, is produced along with other stereoisomeric menthols. *l*-Menthol produced in this way is identical with *l*-menthol isolated from oil of peppermint. The structure of menthol and menthone follows from these reactions:



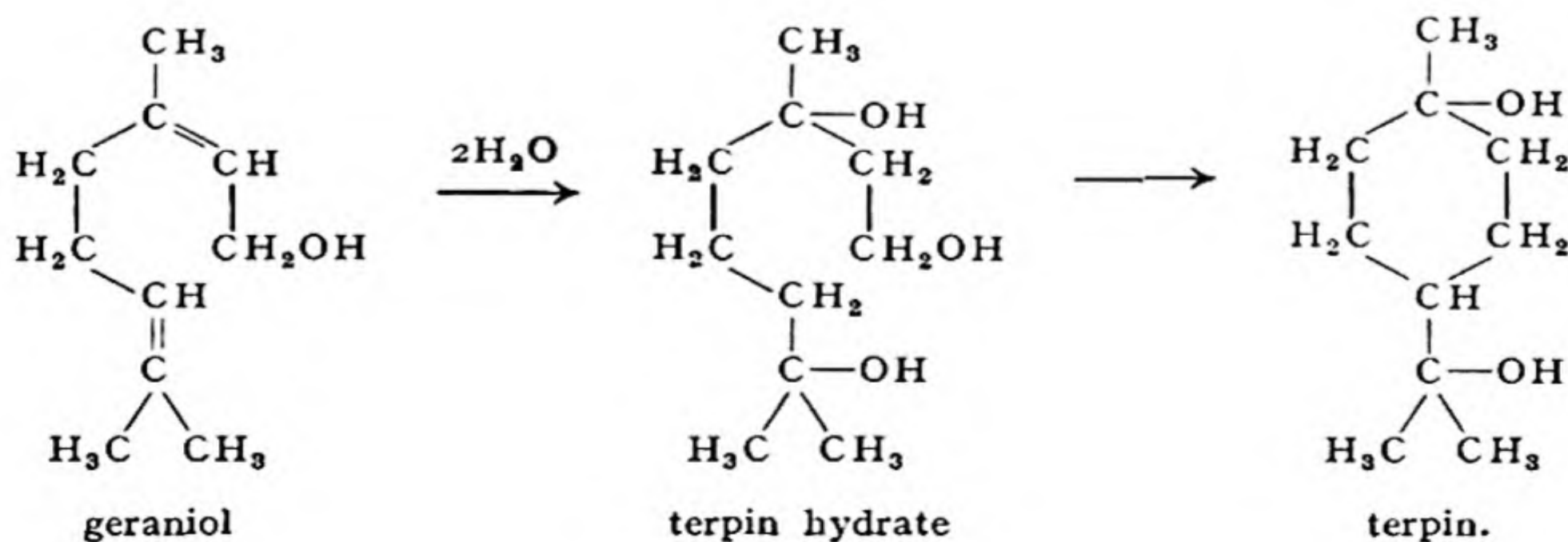
The structure of thymol follows from its degradation into propene and *m*-cresol by heating with phosphorus pentoxide.

According to the above formula, three asymmetric carbon atoms are present in the menthol molecule; hence eight stereoisomers are possible as four pairs of optical antipodes, all of which are known.

Menthol has mild antiseptic properties and is used in medicine and as a component of pharmaceutical products.

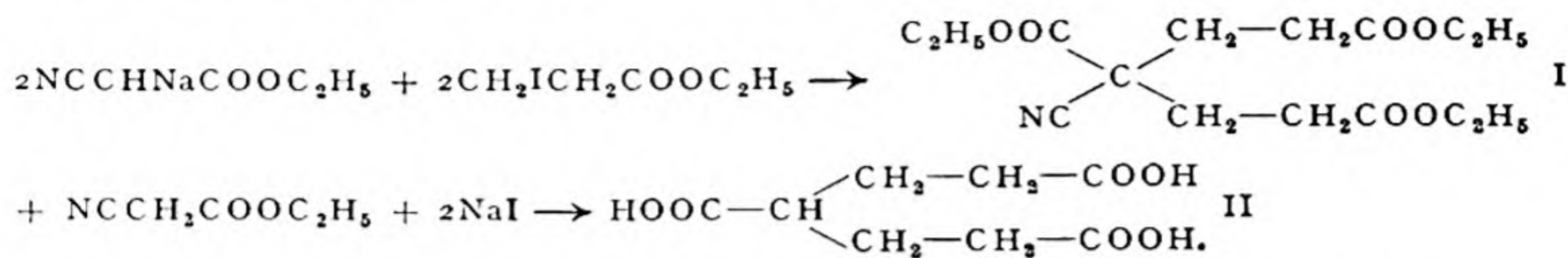
l-Menthone (b.p. 204° , m.p. -7° , $[\alpha]_{\text{D}} = -29.6^{\circ}$) occurs along with *l*-menthol in peppermint oil.

A dihydric alcohol, $C_{10}H_{18}(OH)_2$, *terpin* or *menthane-1,8-diol* (b.p. 258°) can be obtained by treating geraniol (95) with dilute sulphuric acid, when the addition of two molecules of water takes place with the production of *terpin hydrate*. By heating the latter, a molecule of water is eliminated and *terpin* is formed:



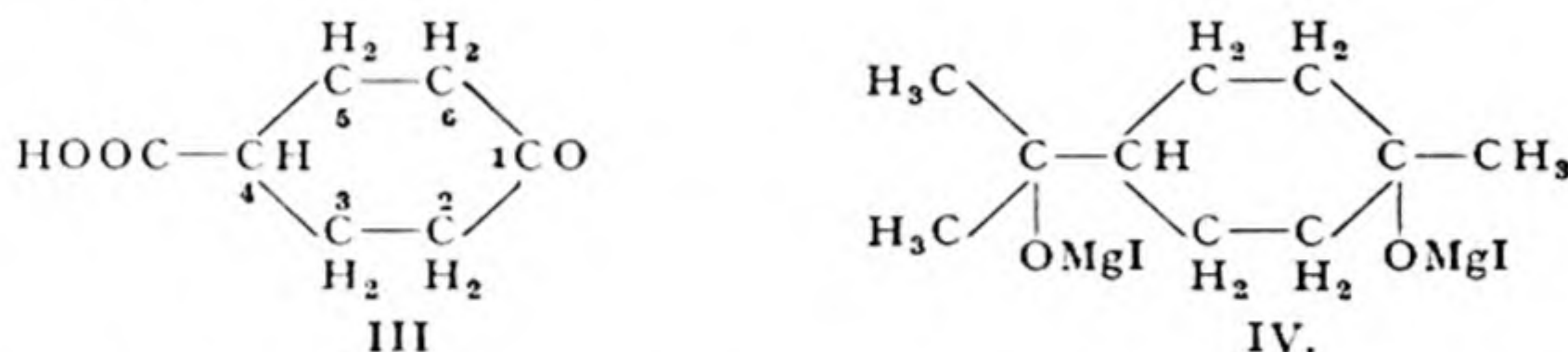
The structure of terpin following from this method of formation, was confirmed by the production of menthane by reducing terpin with hydriodic acid and by the following synthesis due to W. H. PERKIN Jun.

Pentane 1,3,5-tricarboxylic acid (II) was obtained via the compound I, from the sodium derivative of ethyl cyanoacetate (123) and 2-iodopropionic acid:



II is produced from I by hydrolysis and elimination of carbon dioxide.

When compound II is heated with acetic anhydride, water and carbon dioxide are split off with the production of *cyclohexanone 4-carboxylic acid* (III) in accordance with BLANC's rule:

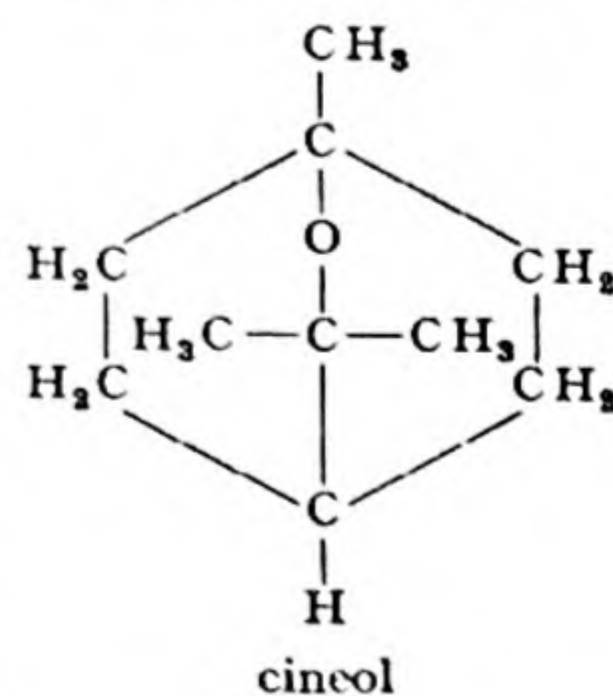


When the methyl ester of this acid is treated with an excess of methylmagnesium iodide, both the ketone carbonyl group and the ester group react to form the compound IV from which terpin (in the *cis*-form) is obtained after decomposition with dilute acid.

According to BLANC's rule, dicarboxylic acids with four or five carbon atoms such as succinic acid, $\text{HOOC}(\text{CH}_2)_2\text{COOH}$, or glutaric acid, $\text{HOOC}(\text{CH}_2)_3\text{COOH}$, give internal anhydrides on heating with acetic anhydride; dicarboxylic acids with six or seven carbon atoms, like adipic acid, $\text{HOOC}(\text{CH}_2)_4\text{COOH}$ or pimelic acid, $\text{HOOC}(\text{CH}_2)_5\text{COOH}$, give cyclic ketones having five or six atoms respectively in the ring, by this treatment.

A *trans*-form of terpin is also known. Terpin does not itself occur in nature; it is prepared on a technical scale by the action of dilute acids on pinene (298) and is used for several purposes including the preparation of terpineol.

By removing water from *cis*-terpin, along with other compounds there is formed an internal anhydride, $\text{C}_{10}\text{H}_{18}\text{O}$. This compound, which is identical with *cineol*, melts at -1° and boils at 174° . Cineol is a constituent of many essential oils and occurs in substantial quantities in eucalyptus oil and in wormseed oil (*oleum cinæ*). On the basis of the method of formation mentioned above, the annexed formula, which has been confirmed by an examination of the oxidation products of cineol, has been assigned to the latter compound.



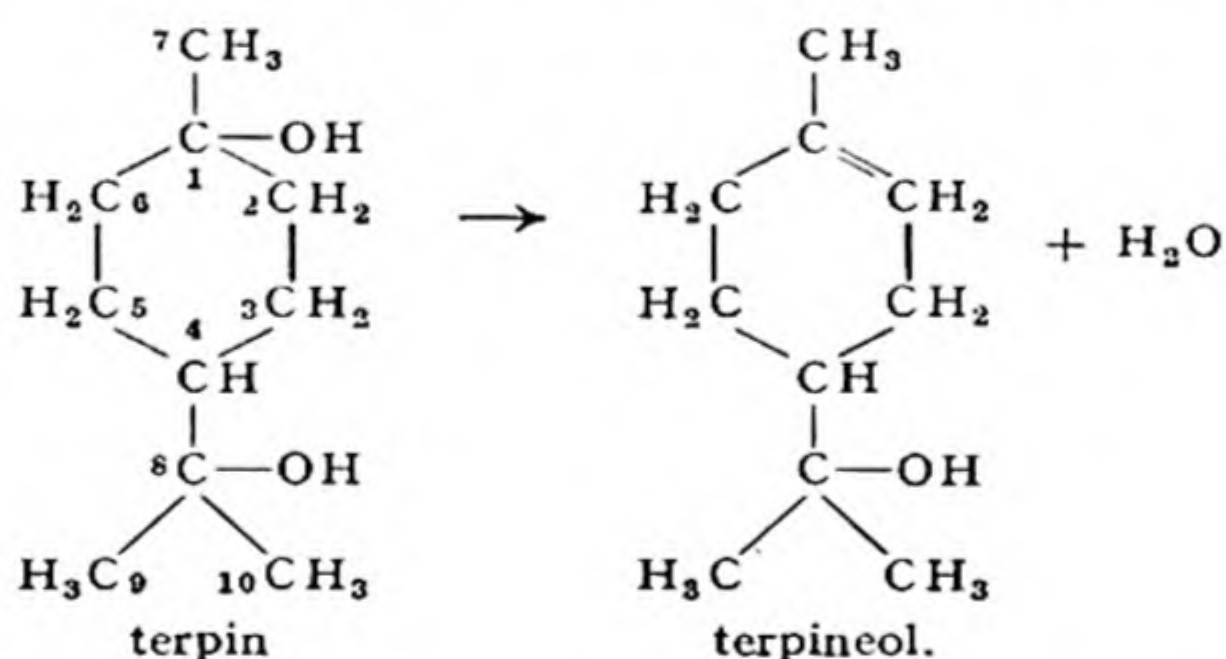
According to this formula, cineol possesses an oxygen atom in an ether-like mode of combination; in agreement with this fact, the substance may be heated with sodium at the boiling point without decomposition. Cineol gives addition products with hydrogen halides which are oxonium salts; these may be used for its isolation and identification.

296. Unsaturated derivatives of menthane. The hydrocarbons, the *menthenes* are of little importance.

Of the various isomeric *unsaturated alcohols*, α -terpineol $C_{10}H_{18}O$, should be discussed. This compound occurs, for example, in *cajéput oil* and *neroli oil*. Both optically active and inactive forms occur in essential oils. Dextro-rotatory terpineol melts at $38-40^\circ$, boils at 220° and has $[\alpha]_D = +95.9^\circ$.

α -Terpineol has an odour reminiscent of that of lilac and is used as a perfume. It is produced along with isomeric alcohols by heating terpin with phosphoric acid whereby a molecule of water is eliminated; this method of preparation is used commercially.

On treatment with dilute sulphuric acid, terpineol is converted into terpin hydrate. Hence the structure of terpineol must be closely related to that of terpin. Since terpineol is known in optically active forms, it follows that in its formation from terpin the hydroxyl group on carbon atom 1 must have reacted with a hydrogen atom on carbon atoms 2 or 6 with the elimination of water, for elimination of water between carbon atoms 8 and 4, 8 and 9 or 8 and 10, would not produce an asymmetric carbon atom:

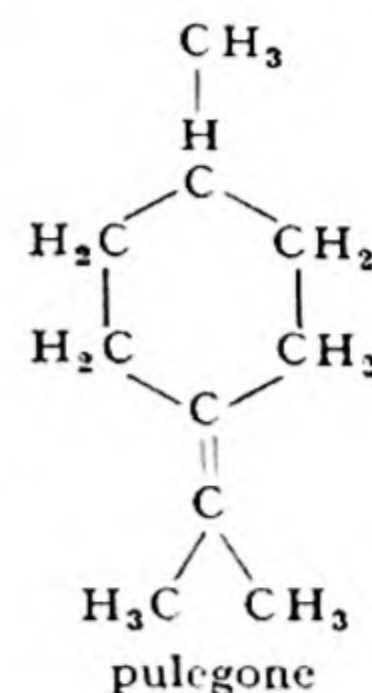


dl-Terpineol was prepared synthetically by W. H. PERKIN Jun. in a similar way to terpin (see page 484).

Unsaturated ketones. *d*-Pulegone $C_{10}H_{16}O$ occurs in various essential oils from species of the labiate family, including *mentha pulegium* (*pennyroyal*) and *hedeoma pulegioides*; it boils at 222° , has $[\alpha]_D = +21^\circ$ and forms an oxime. When submitted to catalytic hydrogenation with platinum black at ordinary temperatures, *d*-pulegone is converted into *menthone*, from which it follows that the oxygen in pulegone is attached to carbon atom 3. The

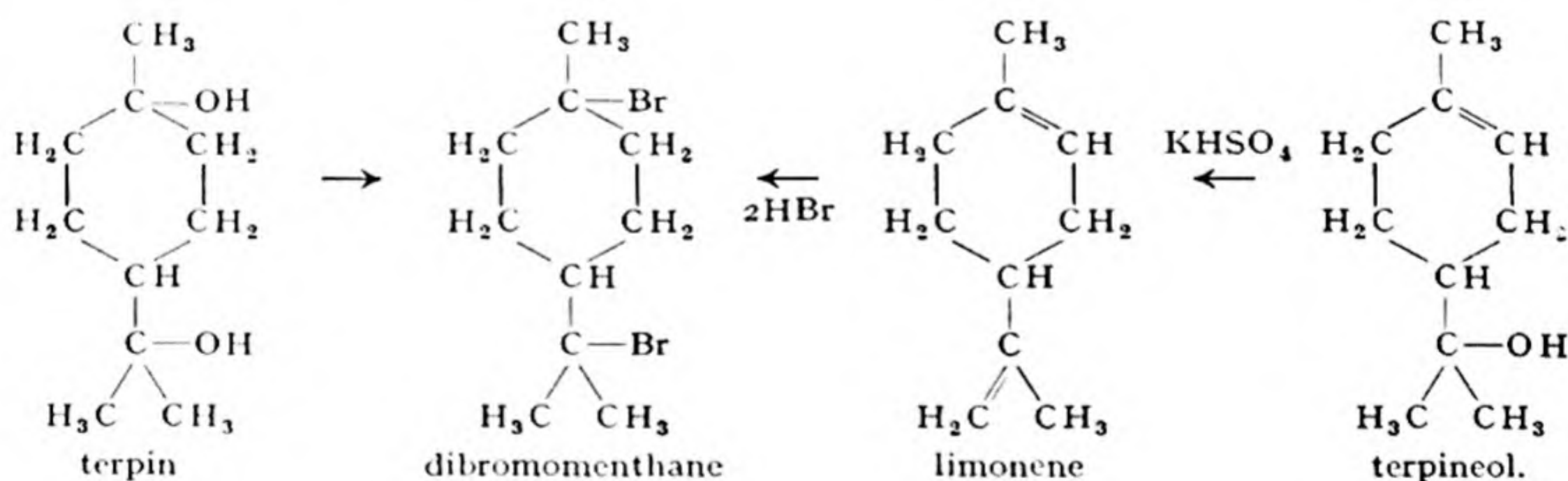
double bond is situated between carbon atoms 4 and 8, since acetone is produced both by oxidation and by heating with water. The formula is therefore as shown here.

297. Menthadienes and their derivatives. Various isomers of the hydrocarbons $C_{10}H_{16}$ are found as constituents of essential oils. *Limonene* occurs as the dextro-rotatory isomer, $[\alpha]_D = +126.8^\circ$, in *caraway oil* and as the laevo-rotatory isomer, $[\alpha]_D = -122^\circ$ in *pine-needle oil*; the racemic mixture, which is also called *dipentene*, occurs in considerable quantities in *turpentine oil*.



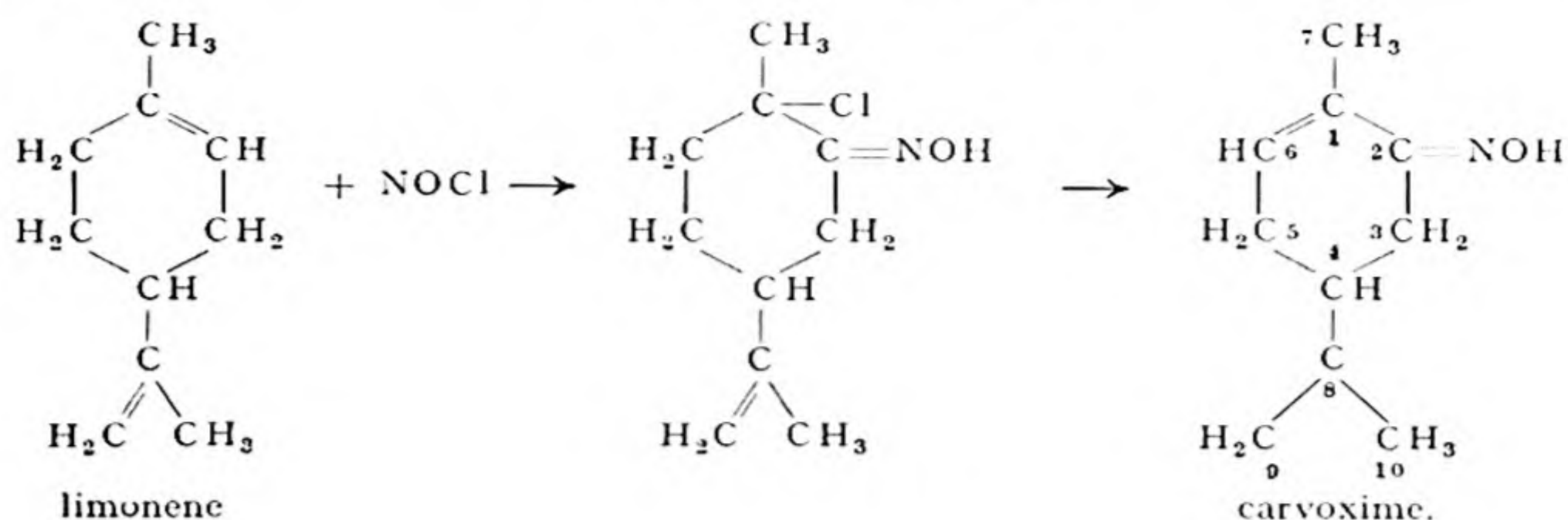
All three isomers boil at 176° . Limonene has a smell like lemons; it gives a crystalline tetrabromide, melting at 105° , and is converted into menthane by catalytic hydrogenation, which indicates the structure of the carbon skeleton.

The positions of the double bonds follow from the reactions described below. Limonene is produced by warming terpineol with potassium bisulphate when a molecule of water is split off. Limonene can also add on two molecules of hydrogen bromide with the formation of a dibromomenthane, which is also produced from terpin by replacing the two hydroxyl groups in this alcohol by bromine:

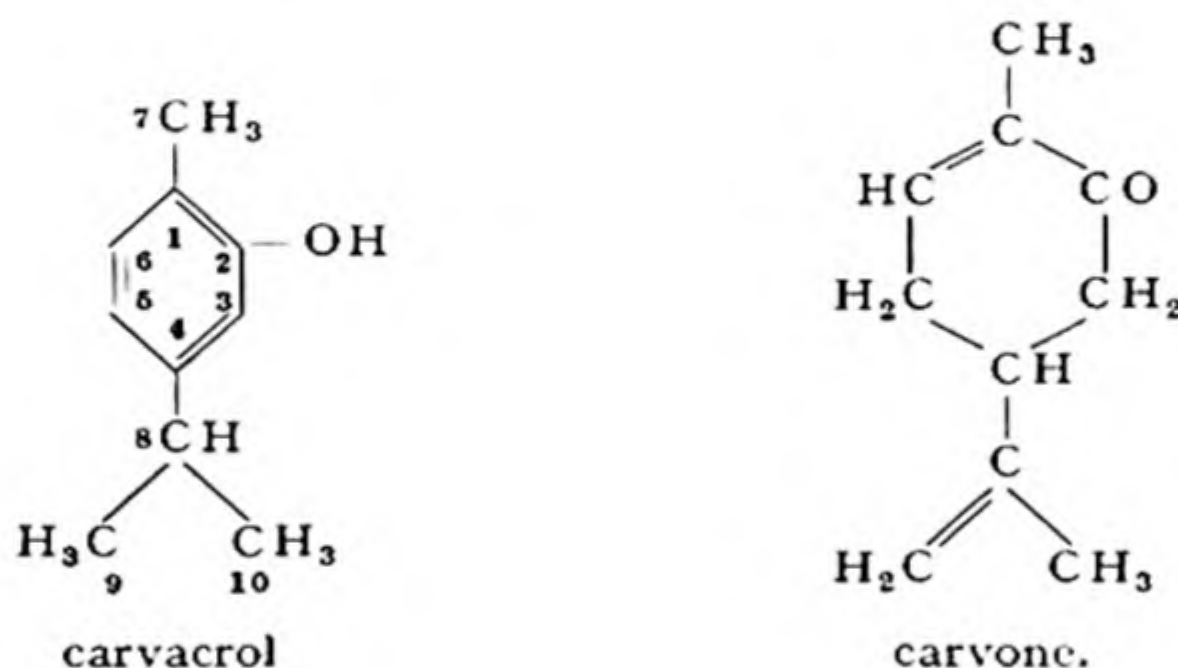


The preparation of isoprene by thermal decomposition of limonene has already been mentioned in 93.

Carvone, $C_{10}H_{14}O$, boils at 230° , the *d*-form occurs in many essential oils and is the main constituent of caraway oil from the fruit of *carum carvi*; the *l*- and *dl*-forms are also found in essential oils. Carvone is a ketone, as appears, for example, from the formation of an oxime (carvoxime). This oxime is produced also when nitrosyl chloride is allowed to add on to limonene and hydrogen chloride is eliminated from the product:

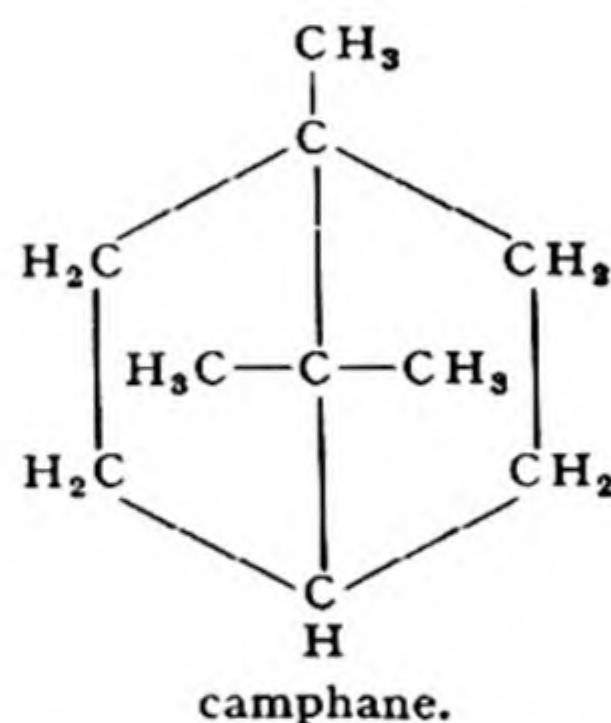
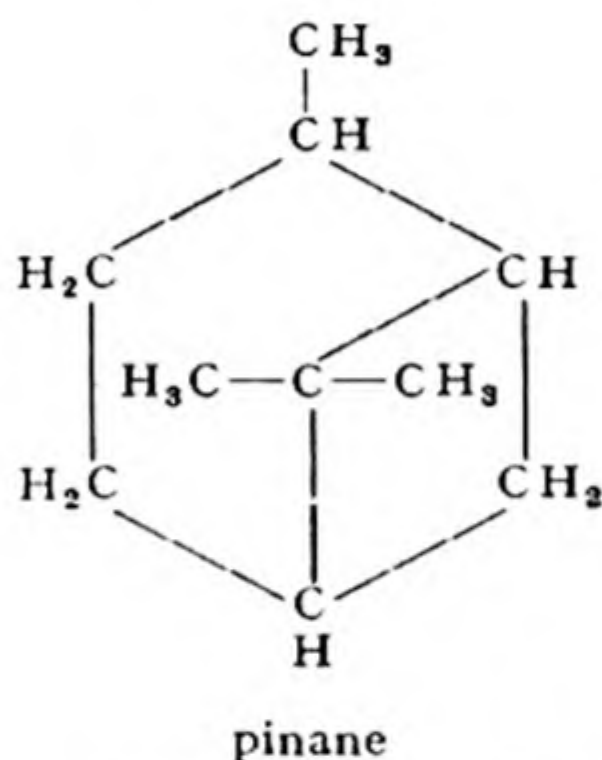
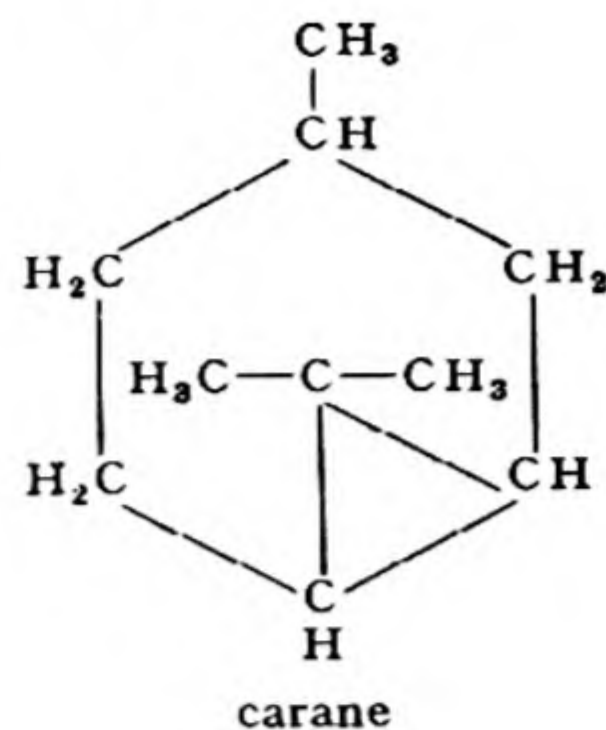
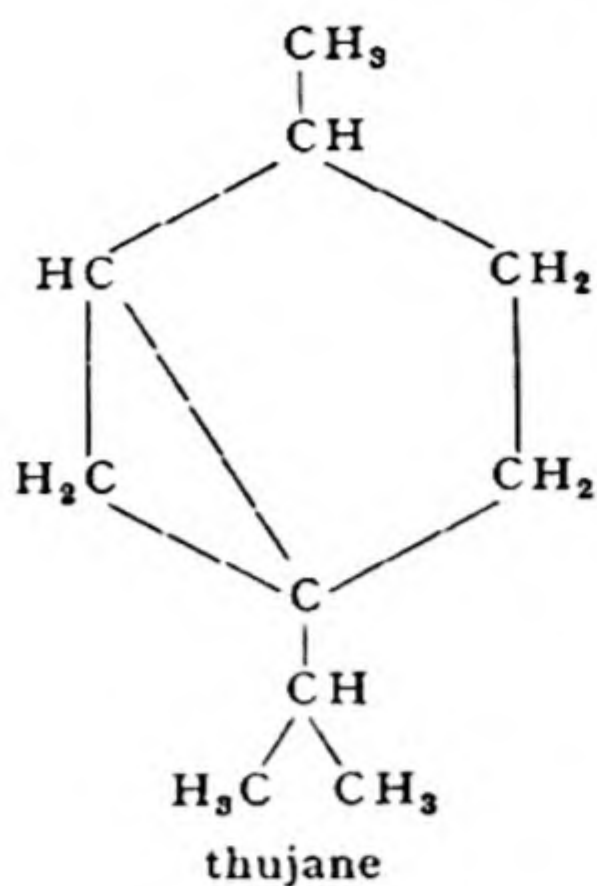


By warming carvone with sulphuric or phosphoric acid, an isomeric compound, *carvacrol*, is formed; this is 2-hydroxycymene, which also occurs in essential oils. When carvacrol is heated with phosphorus pentoxide, propene is split off and *o*-cresol is produced; this establishes its structure. Apart from this method of proving the structure and that of carvoxime, the structure of carvone can be strictly proved by degradation of the molecule:

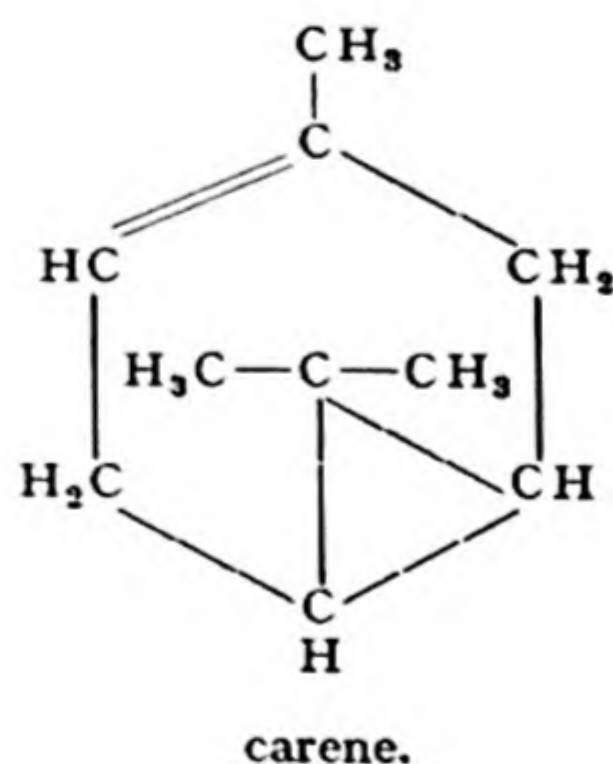
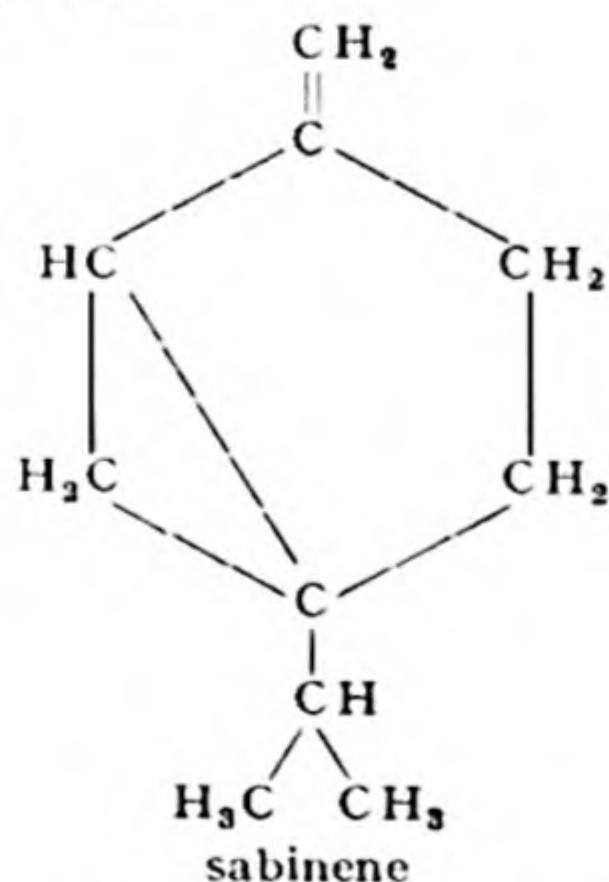


Bicyclic terpenes

298. Among the terpenes there are a number of hydrocarbons of the formula $C_{10}H_{16}$, in which it is possible to assume the presence of only one double bond, because these compounds can take up no more than two mono-valent atoms or groups of atoms in addition reactions. On catalytic hydrogenation, these compounds are converted into hydrocarbons having the composition $C_{10}H_{18}$, which are quite saturated in character. Since they contain two atoms of hydrogen less than the saturated cyclic hydrocarbon, menthane $C_{10}H_{20}$, a second closed chain of atoms must be present in the molecule. Four isomeric hydrocarbons $C_{10}H_{16}$ are known, having the structures shown in the following formulae. There are important derivatives of each of these types:



Thujane, a liquid boiling at 157° , does not occur in nature but is obtained by the catalytic hydrogenation of *sabinene* $C_{10}H_{16}$, which occurs in the essential oil from *juniperis sabina*. Sabinene is a liquid boiling at $160-165^{\circ}$. From an examination of the oxidation products it has been proved that sabinene has the structure given below. The cyclopropane ring in sabinene and other thujane derivatives can easily change into an open-chain. Sabinene can add on two molecules of hydrogen chloride to form 1,4-dichloromenthane:



Carane, a liquid boiling at 169° , does not occur naturally but some of its derivatives do. In the essential oil from *pinus longifolia* (Indian turpentine) there is present a hydrocarbon $C_{10}H_{16}$, *carene*, a pleasant smelling liquid boiling at 170° . It may be

converted into carene by careful hydrogenation in presence of palladium black. The structure of carene is derived from the constitutions of its oxidation products.

Pinane $C_{10}H_{18}$, which boils at 166° , does not itself occur in the vegetable kingdom but it can be readily obtained by catalytic reduction of *pinene*, $C_{10}H_{16}$, the most important hydrocarbon in this group of terpenes.

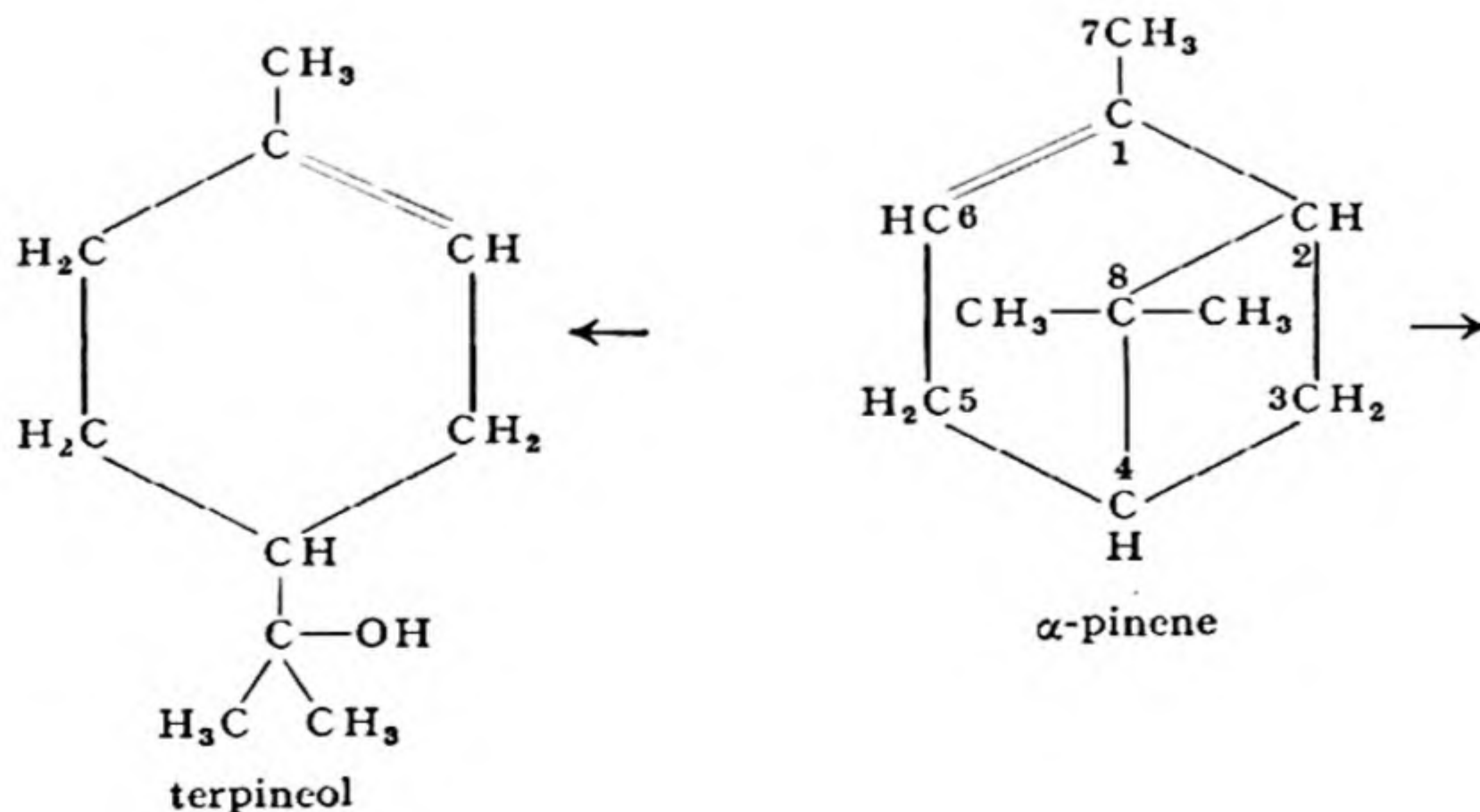
Pinene occurs very widely distributed in the vegetable kingdom; most essential oils from conifers contain pinene and it is the main constituent of turpentine oils.

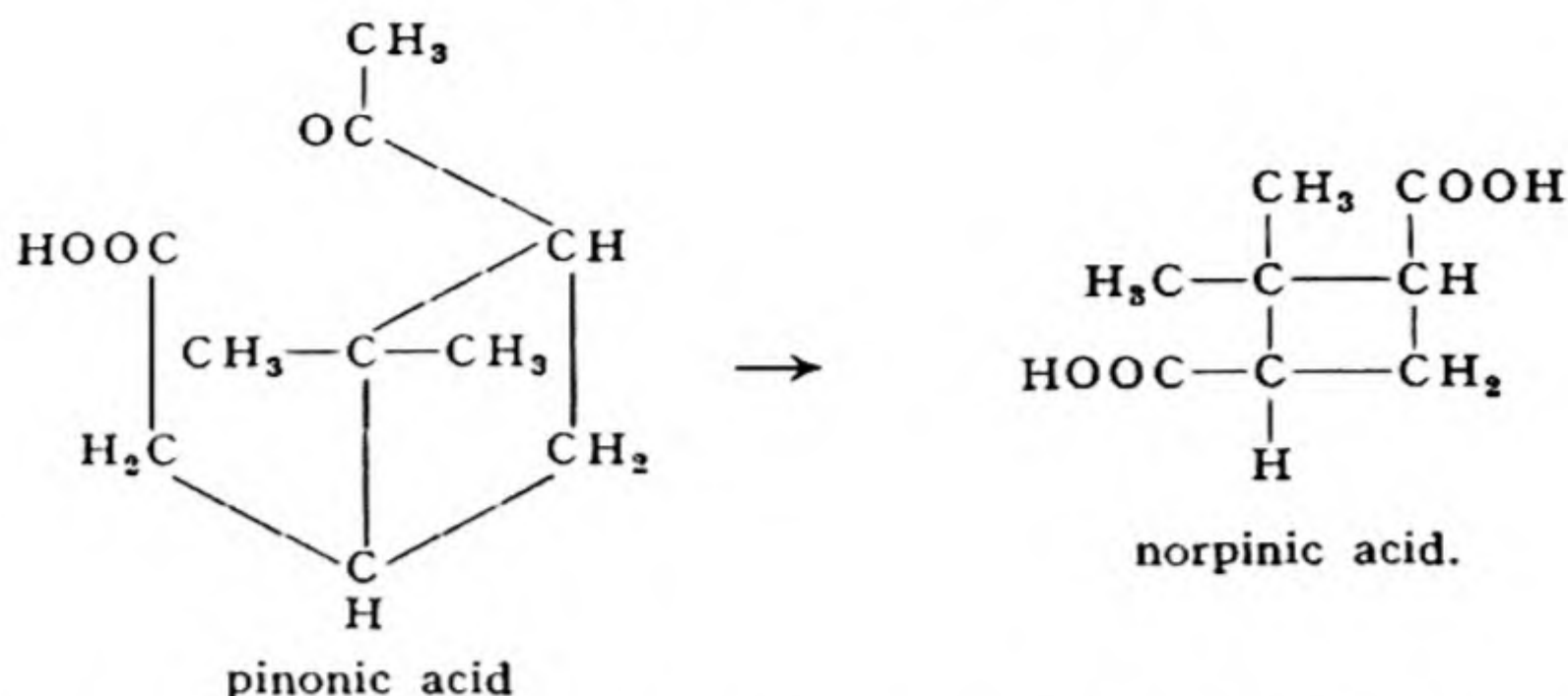
Turpentine is a resinous exudate obtained from various species of pine; when turpentine is distilled in steam, turpentine oil, which may contain up to 90 % of pinene, is obtained. Rosin (*colophony*) remains behind as a residue. Turpentine oil is used as a solvent and for the preparation of paints and lacquers.

Two isomeric pinenes are known, α -*pinene* and β -*pinene*. The mixture of pinenes in oil of turpentine consists mainly of α -pinene, b.p. 156° , $[\alpha]_D = 48.8^\circ$. Both the active and the inactive forms occur in nature. α -Pinene is slowly oxidised by atmospheric oxygen (autoxidation, compare 257) whereby a peroxide is formed initially, which subsequently breaks down into various other oxidation products.

Pinene easily gives an addition product with nitrosyl chloride, $C_{10}H_{16}NOCl$, melting at 104° . Pinene can be regenerated by treating this addition product with aniline and in this way can be obtained in a purer state.

The derivation of the structure of α -pinene cannot be discussed in its entirety in this book. The presence of a cyclobutane ring in the molecule follows from the formation of *pinonic acid* and *norpinic acid*, carboxylic acids of the cyclobutane series, on oxidation:





By the action of benzenesulphonic acid in acetic solution, pinene takes up a molecule of water with the formation of terpineol, the four-ring being opened. This reaction is in accordance with the position of the double bond. By the action of dilute mineral acids on α -pinene, three molecules of water are taken up and terpin hydrate is produced. Terpin is prepared in this way from oil of turpentine.

β -Pinene has the double bond between carbon atoms 1 and 7.

(b) Camphors

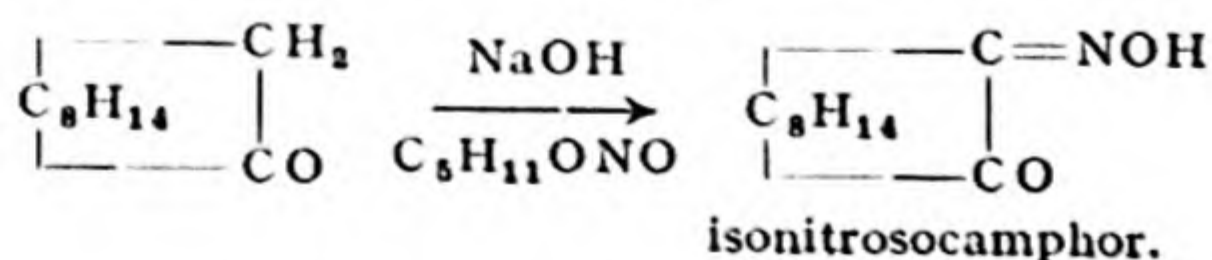
299. In the *camphane* group, ordinary camphor $\text{C}_{10}\text{H}_{16}\text{O}$, is the most important compound; this substance is obtained from the wood of the camphor tree (*cinnamomum camphora*, Japan) by distillation in steam.

d-Camphor has a characteristic smell, forms soft, colourless crystals, melting at 178.7° , boiling at 209° , but sublimes even at ordinary temperatures and has $[\alpha]_D = +44.2^\circ$ in alcoholic solution. The laevo-rotatory form is found in some essential oils.

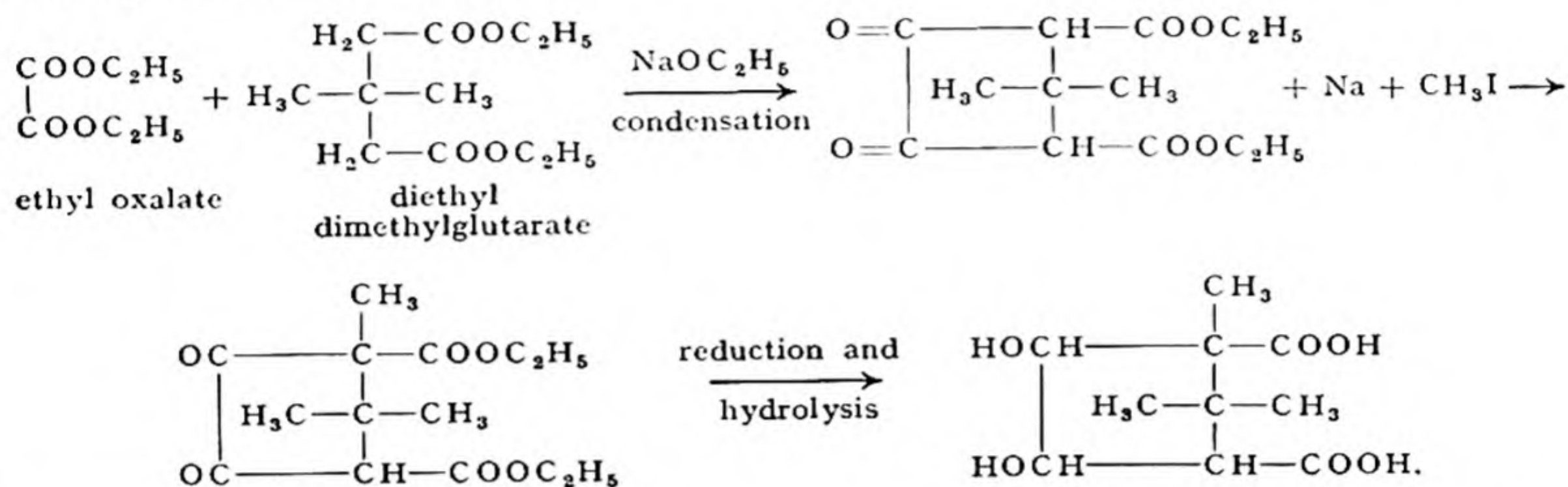
The structure of camphor has been established as the result of extensive and difficult researches by a large number of investigators and only the main points can be mentioned here. Camphor contains a ketone group, as appears from the formation of an oxime and a semicarbazone and from the formation of a secondary alcohol, *borneol*, when camphor is reduced with sodium and alcohol.

From the molecular refraction of camphor, it appears that the molecule contains no double bonds; hence it follows from the formula, $\text{C}_{10}\text{H}_{16}\text{O}$, that the molecule must contain two ring systems.

On treating camphor with amyl nitrite and sodium alcoholate, two hydrogen atoms in the molecule are replaced by the group $=\text{NOH}$; this reaction is specific for compounds in which the group $-\text{CH}_2\text{CO}-$ occurs (146):

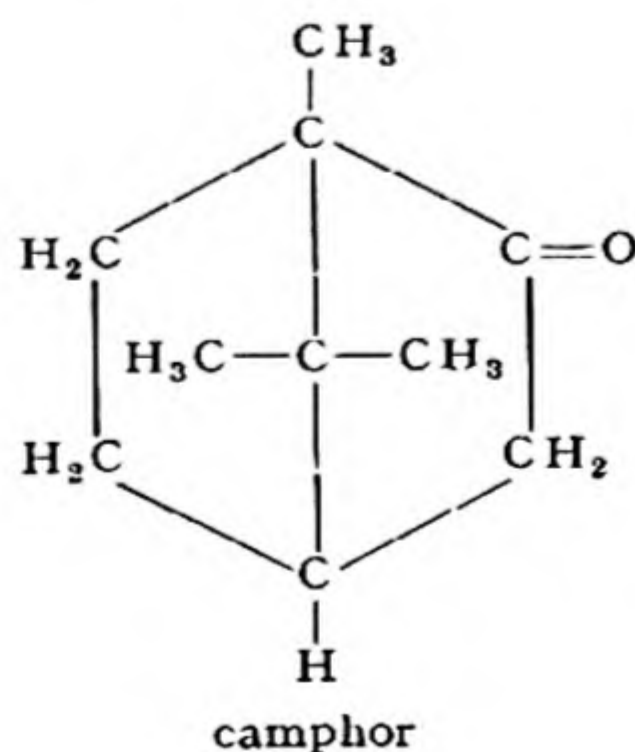
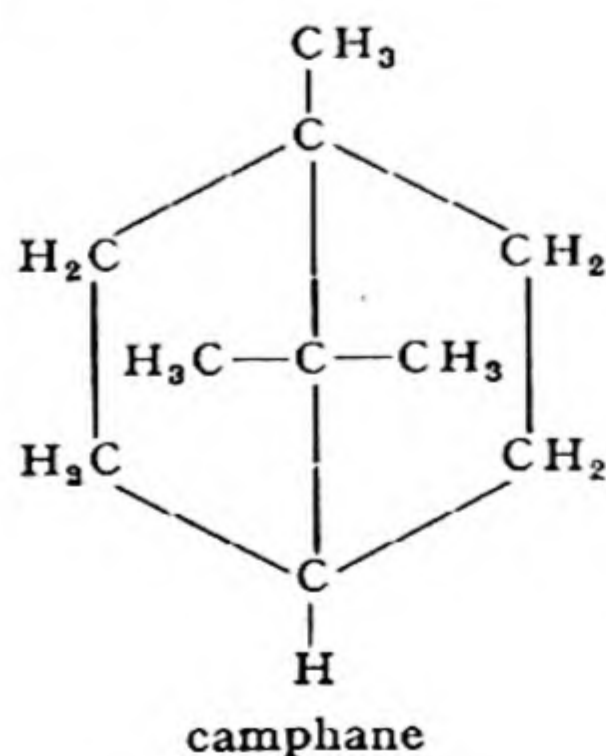


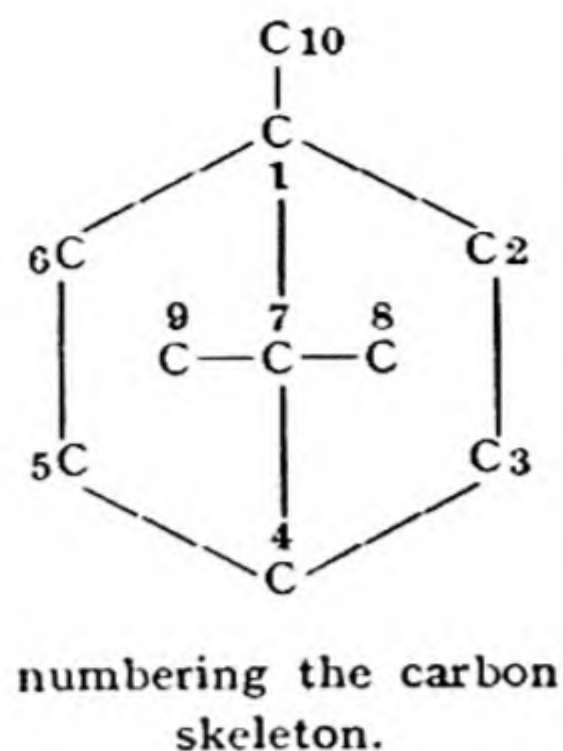
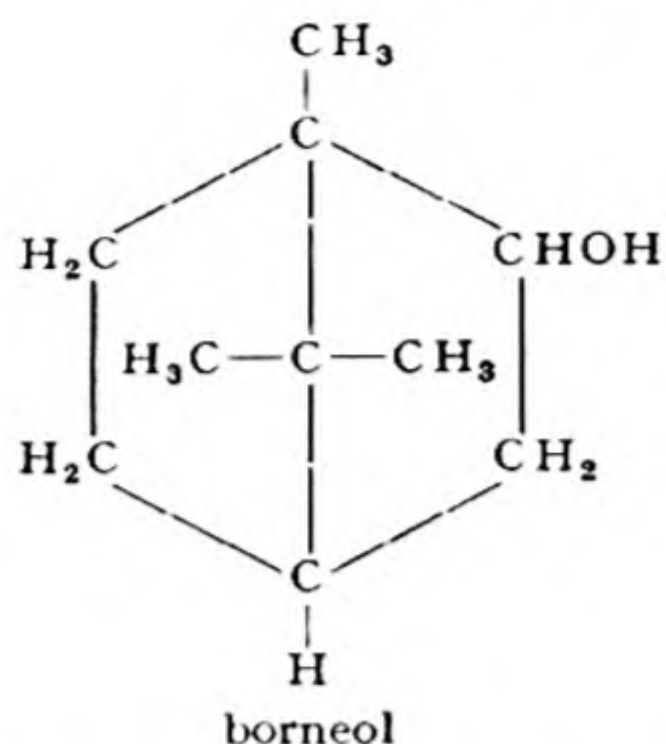
Hydrolysis of *isonitrosocamphor* produces *camphorquinone*, C_8H_{14} $\begin{array}{c} \text{CO} \\ | \\ \text{CO} \end{array}$, which on oxidation with hydrogen peroxide gives *camphoric acid*, C_8H_{14} $\begin{array}{c} \text{COOH} \\ | \\ \text{COOH} \end{array}$ which can also be obtained by oxidising camphor with boiling nitric acid. The structure of camphoric acid, as shown herewith, was deduced by BREDT, from the degradation products of this compound. It was confirmed by synthesis carried out by KOMPPA:



The latter compound can be converted into camphoric acid by replacing the alcoholic hydroxyl groups by bromine and removing the latter by reduction.

According to the structural formula given above, camphoric acid contains two non-identical asymmetric carbon atoms; this is in agreement with the fact that four stereoisomeric, optically active camphoric acids are known, viz. *d*- and *l*-camphoric acid (m.p. 187°) and *d*- and *l*-isocamphoric acid (m.p. 177°). Oxidation of *d*-camphor with nitric acid produces *d*-camphoric acid. The formula for camphor proposed by BREDT is in accordance with that of camphoric acid:



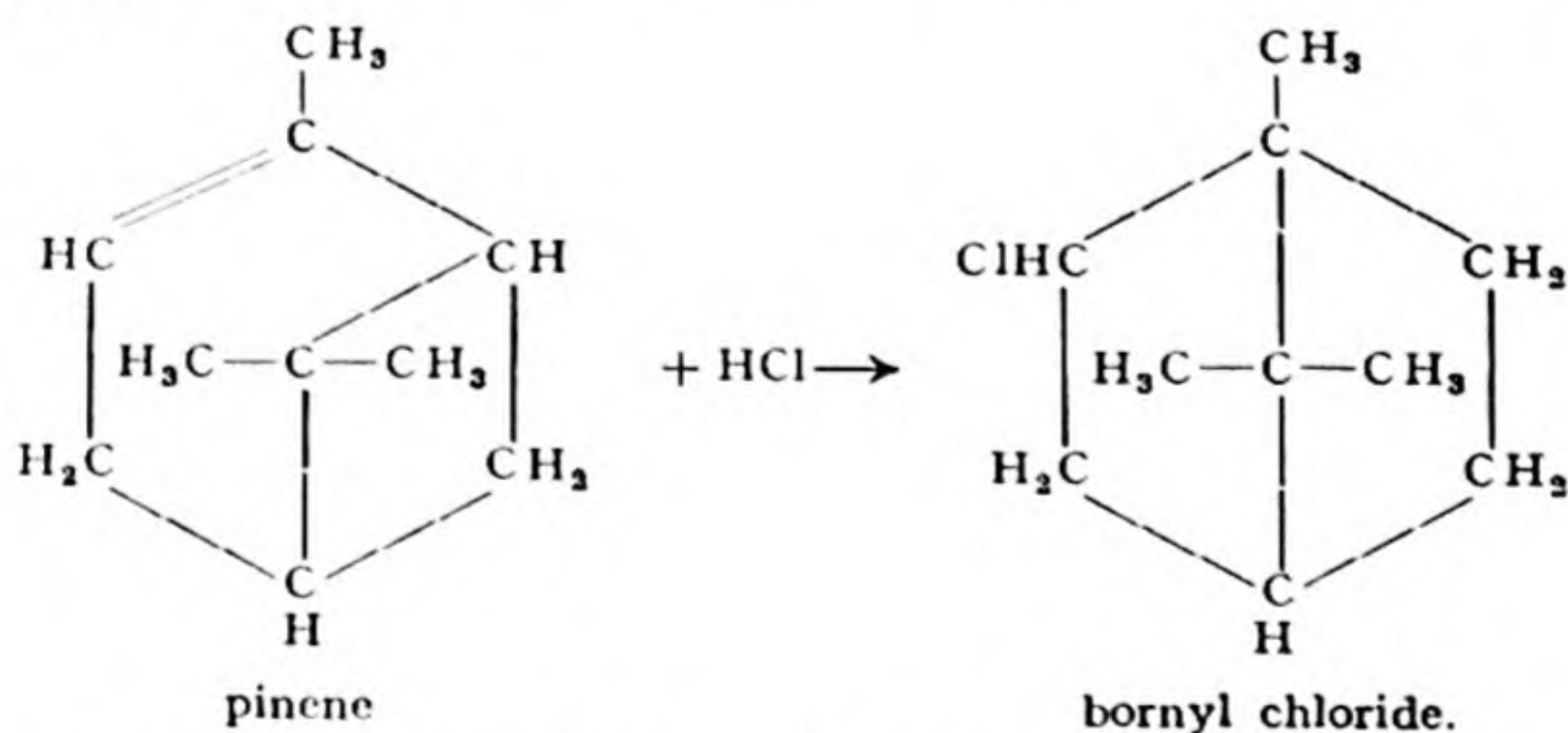


The position of the carbonyl group in camphor follows from the formation of carvacrol (297) on treatment with iodine; hydrogen is removed as hydrogen iodide and isomerisation occurs; the hydroxyl group in carvacrol stands in the *ortho* position with respect to the methyl group. The structure of camphor has been confirmed by synthesis starting from camphoric acid.

The camphor molecule contains two dissimilar asymmetric carbon atoms (1 and 4); from a consideration of models, however, it appears that only two mirror-image forms can exist, since the model of the molecule shows considerable strain for the other pair of mirror-image forms in the carbon chain 1-7-4. In agreement with this conclusion only two optically active kinds of camphor (*d*- and *l*-camphor) are known.

Camphor is used on a large scale for the preparation of celluloid and certain explosives; it is also used for various purposes in medicine.

Camphor is manufactured synthetically on a technical scale from turpentine oil. The pinene present in this material is treated with hydrogen chloride when addition occurs along with an intramolecular transformation, whereby the cyclobutane ring in pinene is converted into the cyclopentane ring of camphane with the production of bornyl chloride:



Camphor can be obtained from bornyl chloride in various ways, *e.g.* by preparing isoborneol from the chloride and oxidising the product.

Borneol, *d*-Borneol or "*borneo-camphor*" is the chief constituent of the essential oil from *Dryobalanops aromatica*; *l*-borneol occurs in the oil obtained from *Blumea balsamifera*; *dl*-borneol is also found in essential oils.

Borneol melts at 198° , boils at 212° and has a camphoraceous smell. *d*-Borneol gives *d*-camphor on oxidation and *l*-borneol, *l*-camphor. It has already been mentioned that *d*-borneol is produced by reducing *d*-camphor with sodium and alcohol; *isoborneol*, m.p. 217° , is the main product obtained in the catalytic hydrogenation of camphor with platinum black. Isoborneol and borneol are *cis-trans*-isomers in which the hydroxyl group is situated *cis*- or *trans*- with respect to the carbon chain 1-7-4.

Camphane $C_{10}H_{18}$ can be obtained by reducing bornyl chloride. This hydrocarbon melts at 154° , boils at 161° and is very volatile even at room temperatures. The camphane molecule is symmetrical as may be seen from the structural formula on page 491; in accordance with this formula, camphane is optically inactive. It does not occur in the vegetable kingdom.

(c) Polyterpenes

300. Of this group, comprising a number of compounds of the composition $(C_5H_8)_n$ ($n > 2$), *caoutchouc* or *rubber* is the most important. This substance is obtained from the milky fluid from various tropical plants, especially from *Hevea brasiliensis*. The milky-looking liquid, *latex*, is coagulated by adding acetic acid, and the coagulum is kneaded between warm rollers and finally rolled out into sheets. This material contains small amounts of by-products as well as the actual rubber. Pure rubber has been obtained by adding alcohol to the colloidal solution of crude rubber in benzene, whereby a precipitate is produced, which can be purified by dissolution in ether and reprecipitation. In this way a colourless, amorphous substance having the composition $(C_5H_8)_n$ is produced.

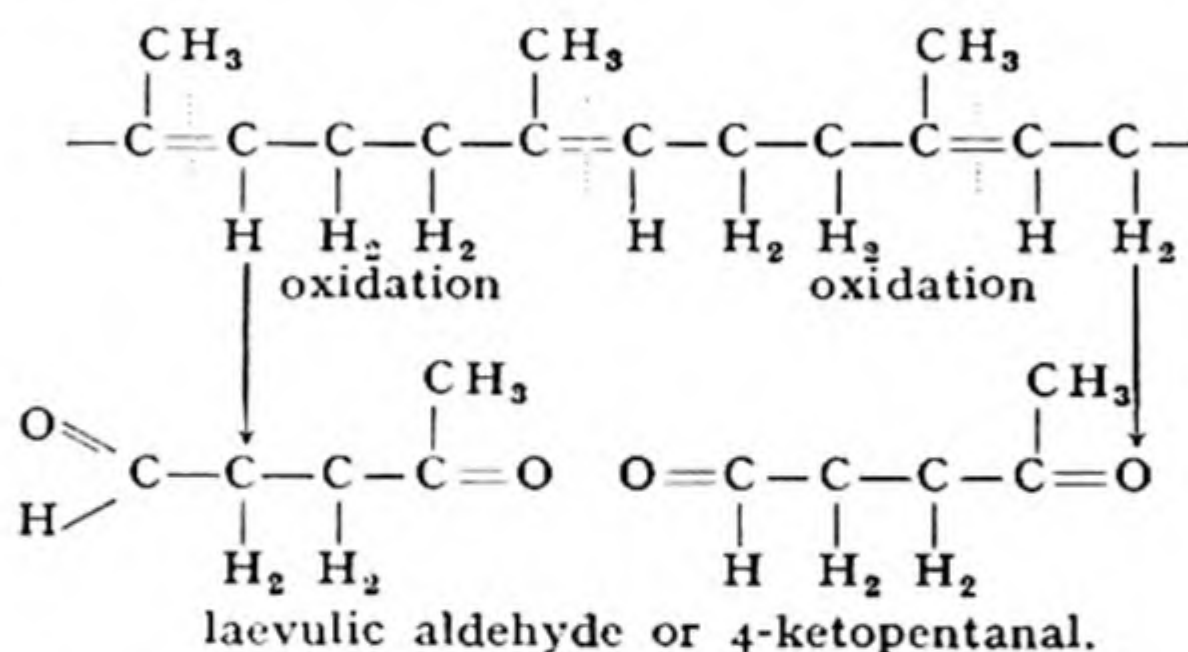
Rubber occurs in two modifications, a soft elastic and a hard non-elastic form. The latter is produced from the soft modification by cooling below 0° or by keeping it for a long time at room temperatures. Consequently rubber loses its elasticity in time. When the hard form is warmed in water, it re-forms the soft modification. X-ray examination has shown that the soft form is amorphous and the hard form crystalline.

J. R. KATZ has found that soft rubber in the unstretched state is amorphous but in the stretched state the X-ray spectrum shows evidence of a crystalline substance. A study of the X-ray diagrams shows that the sub-microscopic crystallites in stretched rubber all lie with the same crystallographic axis parallel with the direction of extension; thus stretched rubber shows a "fibre-like structure". This crystalline orientation disappears on contraction.

Vulcanisation of rubber. Caoutchouc or rubber as such is not useable for most technical purposes. Since it becomes tacky at 30° , it must be vulcanised (GOODYEAR) for the manufacture of pneumatic tyres and numerous other articles. For this purpose, sulphur (about 10 %) is added after the rubber has been made plastic by milling on warm rollers; when this mixture is heated to 140° it loses its plasticity and is converted into vulcanised rubber, which is more elastic and more resistant to all kinds of influences than the original caoutchouc. Well vulcanised rubber can be stretched to ten times its original length without breaking and assumes its original form again on contraction. When the plastic mixture is heated for a longer time with still more sulphur (30 %), it is converted into *ebonite*.

301. Structure of rubber. On catalytic hydrogenation at ordinary temperatures in the presence of platinum and hexahydrotoluene as solvent, rubber takes up two atoms of hydrogen (based on the formula C_5H_8) and is converted into a substance $(C_5H_{10})_n$ (PUMMERER). It can add on iodine monochloride in solution in carbon disulphide, one molecule of ICl adding to each C_5H_8 group. From this it follows that rubber is an unsaturated compound in which there is one double bond per C_5H_8 group. When rubber is treated with ozone, an ozonide having the approximate composition $(C_6H_8O_3)_n$ is produced. Laevulic aldehyde (4-ketopentanal) and laevulic acid (148) are produced in a yield representing 90 % of the theoretical quantity, when the ozonide is decomposed with water (HARRIES, PUMMERER).

From this it follows that there is a chain with the following structure in the rubber molecule:



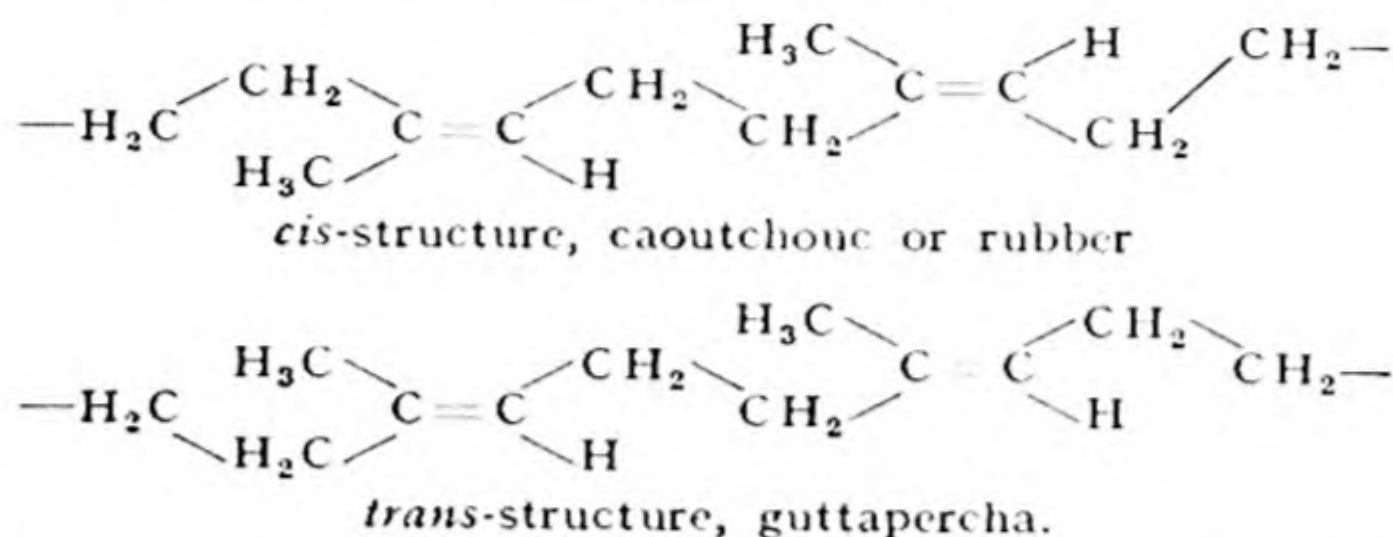
It will be noticed that the isoprene unit is repeated a number of times along the chain.

It had long been known, that various hydrocarbons, including limonene (297) and isoprene (93), are produced in the pyrogenic decomposition of rubber (BOURCHARDAT, GREVILLE WILLIAMS).

In all probability, caoutchouc or rubber does not consist of a single molecular species but is a mixture of closely related hydrocarbons $(C_5H_8)_n$. The mean molecular weight of this mixture of polymer homologues (cf. 103) is undoubtedly very high. Very divergent values are obtained by different methods of determination. It is not yet known with certainty whether the molecules $(C_5H_8)_n$ consist of long open chains or cyclic chains containing a very large number of carbon atoms.

It might be concluded that the presence of one double bond per C_5H_8 group points to a ring structure, for it should be found that rather more than one molecule of hydrogen or iodine monochloride per C_5H_8 group adds on for an open chain with a large number of carbon atoms. However, the longer the carbon chain, the less is the difference from one molecule per C_5H_8 group in the amount of hydrogen or iodine monochloride which will react, so that these experiments are not conclusive.

Guttapercha. The chief component of this material is a hydrocarbon $(C_5H_8)_x$ from which the same degradation products are obtained as from caoutchouc; it is assumed therefore that the molecule of guttapercha consists, like that of caoutchouc, of a chain of isoprene units. From X-ray examination it can be concluded that guttapercha and caoutchouc or rubber hydrocarbon are to be regarded as stereoisomers. In caoutchouc the $—CH_2CH_2—$ groups are situated in the *cis*-position with respect to the double bond and in guttapercha they are in the *trans*-position:



X-ray examination of the hydrocarbon from *balata* shows that it is closely related to that of guttapercha. In all probability the molecules differ in the lengths of the carbon chains.

302. Synthetic rubbers. Although it is possible in various ways to obtain polymerides with high mean molecular weights from isoprene, so far it has not been possible to prepare a synthetic product agreeing entirely in properties with rubber. These polymers, when in the stretched state, do not show the characteristic fibre diagram shown by rubber when examined with X-rays. On vulcanisation they give products which are inferior to vulcanised rubber.

Substitutes for rubber, *i.e.* synthetic rubbers, are prepared on a large scale by polymerising butadiene or dimethylbutadiene, or in some cases, by copolymerisation with styrene (103). Sometimes these materials are superior to rubber for particular purposes on account of their special properties, such as resistance to petroleum distillates (see also 91 for *neoprene*).

(iii) STEROIDS

(a) Sterols; bile acids

303. The *sterols*, which are also known as *sterins*, form a group of compounds very widely distributed throughout the plant and animal kingdoms. They are unsaturated alcohols of rather high molecular weight, which may be compared with the polyterpenes as far as their elementary composition is concerned (ratio of carbon to hydrogen).

Of the animal sterols or *zoösterols*, *cholesterol* or *cholesterin* $C_{27}H_{46}O$ is the most important compound; it forms a normal constituent of the cells of vertebrate animals. The brain and nerve fibres contain considerable quanti-

ties of cholesterol, which also occurs, partly in the form of esters, in other tissues and in blood.

Cholesterol, so named by CHEVREUL from its occurrence in bile ($\chi\omicron\lambda\eta$ = bile, $\sigma\tau\epsilon\alpha\rho$ = fat), can be isolated from gall-stones or from the spinal cord of cattle. It forms colourless crystals, m.p. 148.5° , which are insoluble in water but soluble in a number of organic solvents like ether, benzene, chloroform and warm alcohol. It is optically active $[\alpha]_D = -31.1^\circ$ (in ether). The palmitate and stearate esters of cholesterol form *wool-fat* or *lanoline*, which can be emulsified with water and therefore finds application in the manufacture of ointments and skin creams.

Coprosterol ($\kappa\omicron\pi\rho\omicron\varsigma$ = dung) $C_{27}H_{48}O$ occurs in the faeces of men and carnivorous animals; it melts at 102° , is insoluble in water but soluble in chloroform, ether, ethanol and benzene. It is optically active $[\alpha]_D = 23.5^\circ$ (in chloroform).

The vegetable sterols or *phytosterols* are normal constituents of plant cells and occur in small quantities in vegetable oils; in this connection mention may be made of *stigmasterol* $C_{29}H_{48}O$, which can be isolated from soyabean-oil and the *sitosterols* $C_{28}H_{50}O$, which are widely distributed throughout the vegetable kingdom.

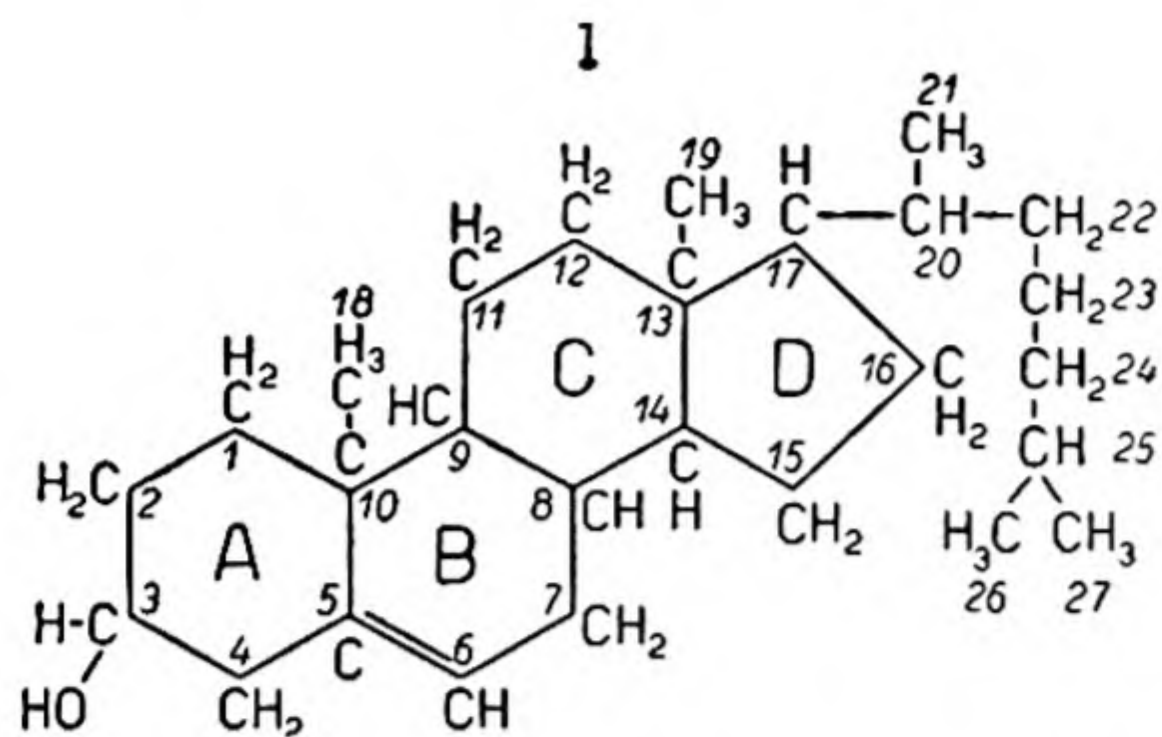
Ergosterol $C_{28}H_{40}O$, occurs in fungi, *e.g.* in a number of yeasts, and was first isolated from ergot (TANRET).

The *bile-acids*, which occur in the bile of vertebrate animals in the form of sodium salts of peptide-like compounds of taurine, $H_2NCH_2CH_2SO_3H$, or glycine (195), are related chemically to cholesterol.

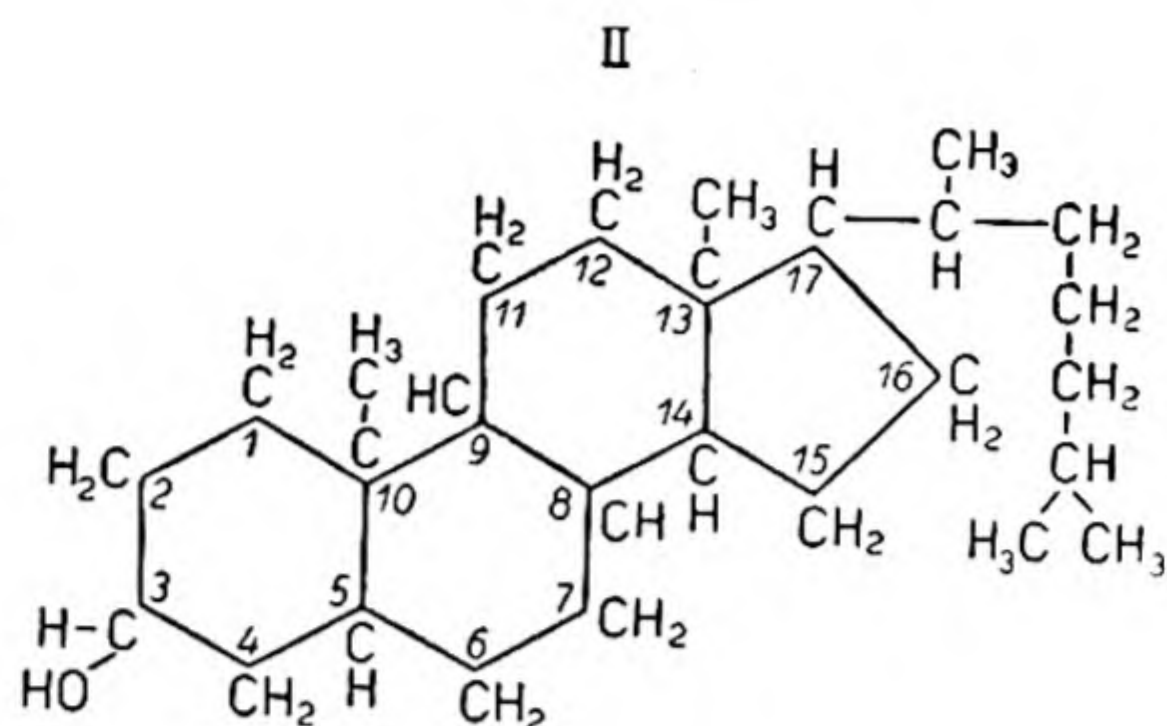
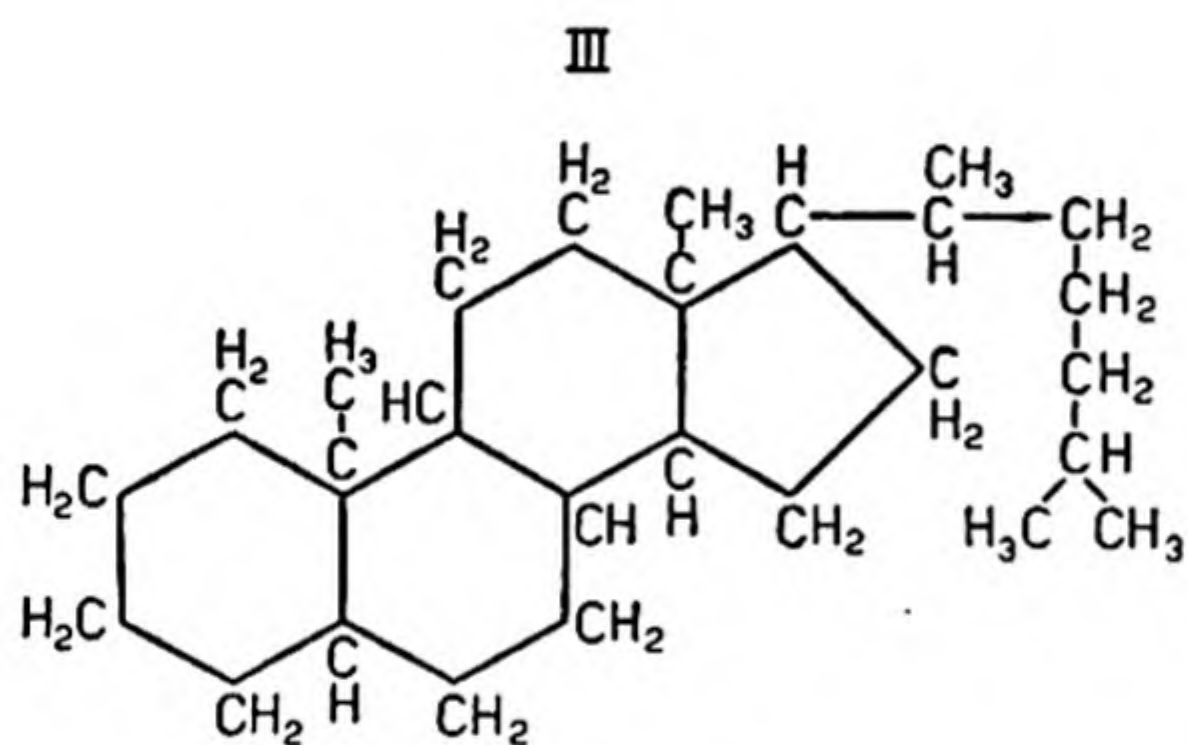
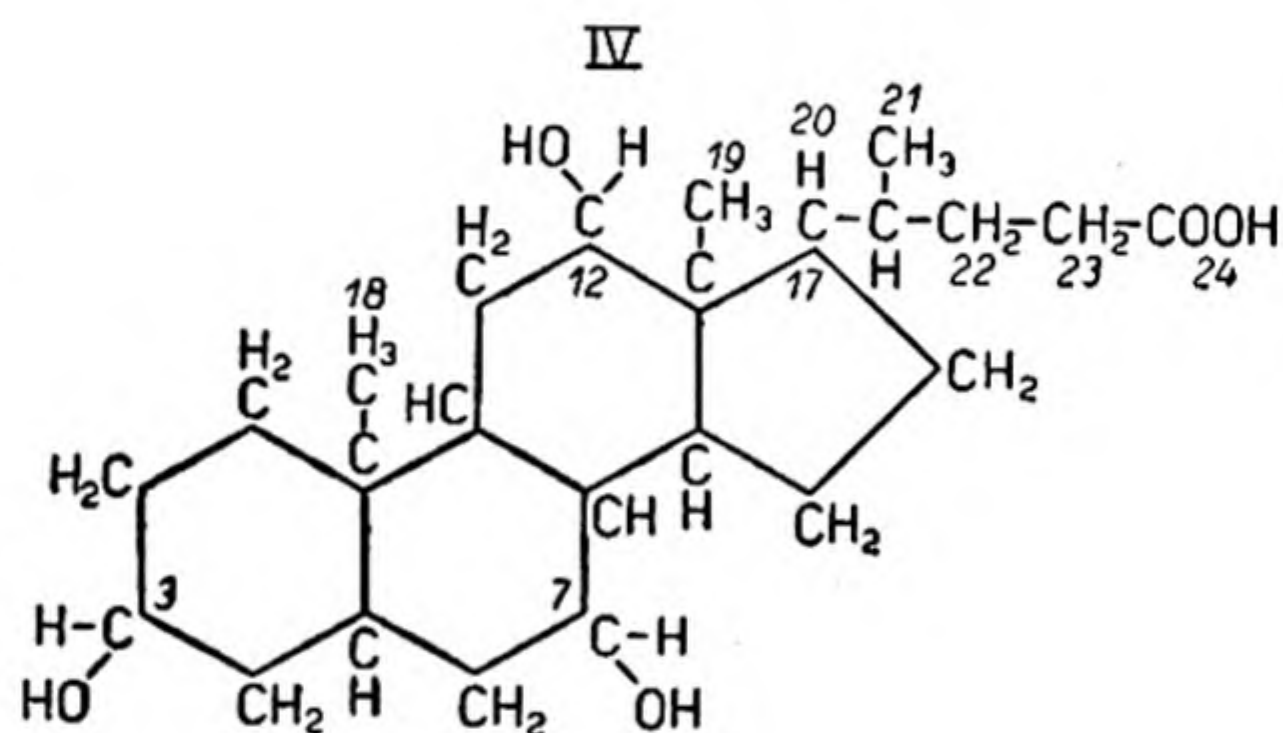
Cholic acid $C_{24}H_{40}O_5$, the most important bile-acid, is the chief constituent of the mixture of bile-acids from human or ox gall-bladders. It melts at $196-198^\circ$ and is sparingly soluble in cold water but readily soluble in ether and ethanol. The alkali salts are readily soluble in water. Cholic acid is optically active $[\alpha]_D = 31.5^\circ$ (in alcohol).

Other physiologically important substances like the D-group vitamins, the sex-hormones and a number of hormones in the suprarenal glands are related to cholesterol in chemical structure. These compounds are denoted by the general name *steroids*.

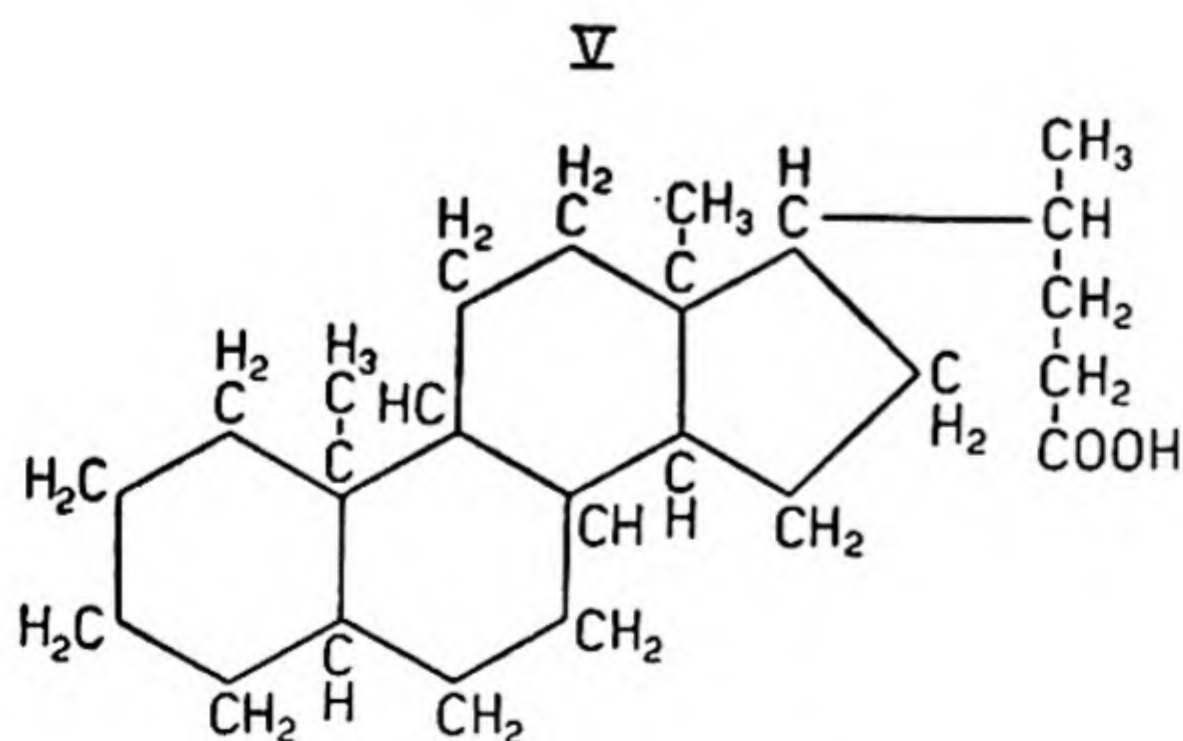
The chemical structure of a number of these compounds has been elucidated, mainly during the period 1910-1935, by the researches chiefly of WIELAND, WINDAUS, RUZICKA, ROSENHEIM, DIELS, JACOBS, REICHSTEIN and their collaborators. It would be impossible in a book of this size to give the complete proof of the structures of the most important members of this group. In this connection, however, the most important experimental data, which have led to the structure of cholesterol and cholic acid, will be discussed on the basis of the structural formulae given on page 497.



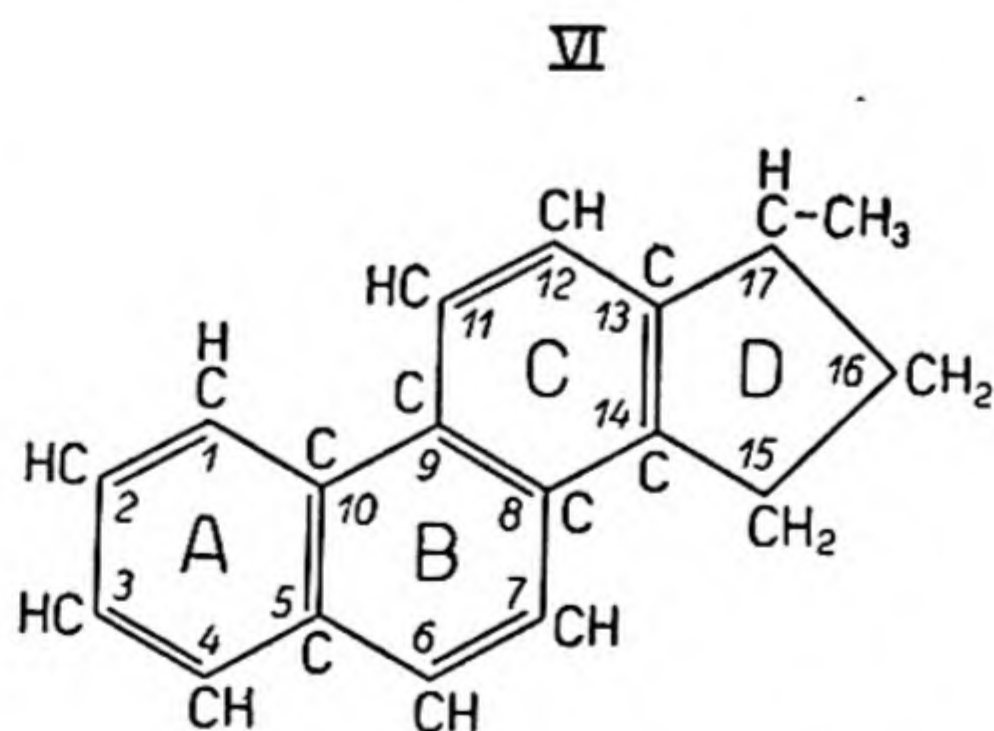
Cholesterol

(Coprosterol) *cis-trans*-
(Cholestanol) isomers(Coprostanane) *cis-trans*-
(Cholestane) isomers

Cholic acid



Cholanic acid

Methylcyclopentanophenanthrene $C_{15}H_{18}$

304. *Structure of cholesterol* (see formula I). The cholesterol molecule contains an alcoholic hydroxyl group (as follows from the formation of esters with organic acids) and a $>C=C<$ bond as is shown by the addition of one molecule of bromine or hydrogen chloride. Catalytic hydrogenation of cholesterol produces an alcohol $C_{27}H_{48}O$, *cholestanol* (II), which is saturated in character. If this hydroxyl group in cholestanol is replaced by chlorine and the resultant compound treated with sodium and amyl alcohol, a hydrocarbon $C_{27}H_{48}$ cholestane (III) is produced, which must have the same carbon skeleton as cholesterol from its method of preparation. This hydrocarbon is saturated in character but contains eight atoms of hydrogen less than an alkane with 27 carbon atoms ($C_{27}H_{56}$). From this it follows that the cholestane molecule must contain *four carbon rings*, it being undecided for the moment whether these rings are condensed or not. On oxidising *cholestanyl acetate* with chromic acid or nitric acid, there are produced amongst other things a ketone, which appears to be identical with 6-methylheptan-2-one, $CH_3COCH_2CH_2CH_2CH(CH_3)_2$, and a compound $C_{19}H_{30}O_2$.

Together these two oxidation products contain 27 carbon atoms, *i.e.* the same number as cholestanol. Cholestanol (and also cholesterol) must therefore possess a side-chain of eight carbon atoms, from which 6-methylheptan-2-one can be produced by oxidation *i.e.* the 20–27 chain in formula I. The compound $C_{19}H_{30}O_2$ contains a ketonic group (formation of a semicarbazone) and a hydroxyl group (formation of an acetate). The hydrocarbon from which this hydroxyketone will be derived, must therefore have the composition $C_{19}H_{32}$, *i.e.* it must contain four rings.

On heating cholesterol with selenium to 320° , decomposition occurs with the formation of water, hydrogen selenide and a mixture of hydrocarbons. From this reaction mixture a hydrocarbon $C_{18}H_{16}$ can be isolated in small yield, the structure of which has been established synthetically as *17-methylcyclopentanophenanthrene* (VI) containing four condensed rings (211). Many compounds containing cyclohexane rings in their molecules react on heating with selenium in such a way that the cyclohexane rings are converted into aromatic rings; the selenium has a “dehydrogenating” action since it extracts hydrogen from the molecule and forms therewith hydrogen selenide. Cyclopentane rings on the other hand are not dehydrogenated by selenium. Further, it appears that on dehydrogenation with selenium, quaternarily combined methyl groups are split off probably as methane; in the cholesterol molecule these are the methyl groups 18 and 19. It is clear that rings A and B in cholesterol can be converted into aromatic rings only if the methyl groups attached to carbon atoms 10 and 13 are split off.

This same methylcyclopentanophenanthrene is also produced in the dehydrogenation of cholic acid (IV) by selenium. Before these researches

had been carried out, the structure of the tetracyclic ring-system had in the main been deduced from an examination of the compounds produced in the oxidative degradation of cholesterol and the bile acids.

From the following it appears that the hydroxyl group in cholesterol is attached to a carbon atom situated in a ring. By oxidising cholestanol with chromic acid, cholestanone $C_{27}H_{46}O$ is produced, which has the properties of a ketone. When cholestanone is oxidised more vigorously, a dicarboxylic acid $C_{25}H_{44}(COOH)_2$ is produced; since this contains the same number of carbon atoms as cholestanone, the carbonyl group in the latter compound must be incorporated in a ring (cf. the oxidation of cyclohexanone 287) and the same argument holds for the $CHOH$ group in cholesterol.

On heating with acetic anhydride the dicarboxylic acid $C_{25}H_{44}(COOH)_2$ gives a cyclic ketone $C_{25}H_{44}CO$. From BLANC's rule (295) it is concluded that the carboxyl groups in the dicarboxylic acid are separated by a chain of four carbon atoms, so that the ring containing the hydroxyl group in cholesterol must be a six-ring.

From a comparative examination of the oxidation products of cholesterol and its derivatives, it is concluded that the hydroxyl group must be situated on carbon atom 3 and the double bond between carbon atoms 5 and 6. The positions of the methyl groups on carbon atoms 10 and 13 follows from a comparative examination of the degradation products of cholesterol and various bile-acids.

Structure of coprosterol, cholic acid and cholanic acid. Coprosterol $C_{27}H_{48}O$ (II) shows the properties of a saturated secondary alcohol; the $CHOH$ group forms part of a ring as is proved in the same way as for cholestanol. When the hydroxyl group in coprosterol is replaced by chlorine and the chloride so obtained is reduced, a hydrocarbon $C_{27}H_{48}$ is produced, which is very similar to cholestane but has a lower melting point. Cholestane and copropane (III) are stereoisomers; this is a case of *cis-trans*-isomerism, since the hydrogen atom on carbon atom 5 can be situated in the *cis*- or *trans*-position with respect to the methyl group on carbon atom 10 (compare *cis*- and *trans*-forms of decahydronaphthalene on page 456).

Cholic acid $C_{24}H_{40}O_5$ (IV) is a trihydroxy-mono-carboxylic acid, the esters of which can be converted into triacetyl derivatives. By careful oxidation of cholic acid there is produced a triketonic acid as is shown by reaction with hydroxylamine. Hence cholic acid contains three $CHOH$ groups. By heating cholic acid in a vacuum, three molecules of water can be split off with the formation of a carboxylic acid with three double bonds, *cholatriene carboxylic acid* $C_{24}H_{34}O_2$. This acid is converted by catalytic hydrogenation into a saturated carboxylic acid *cholanic acid* $C_{24}H_{40}O_2$ (V). Among the products which are obtained when cholesterol and its derivatives are oxidised

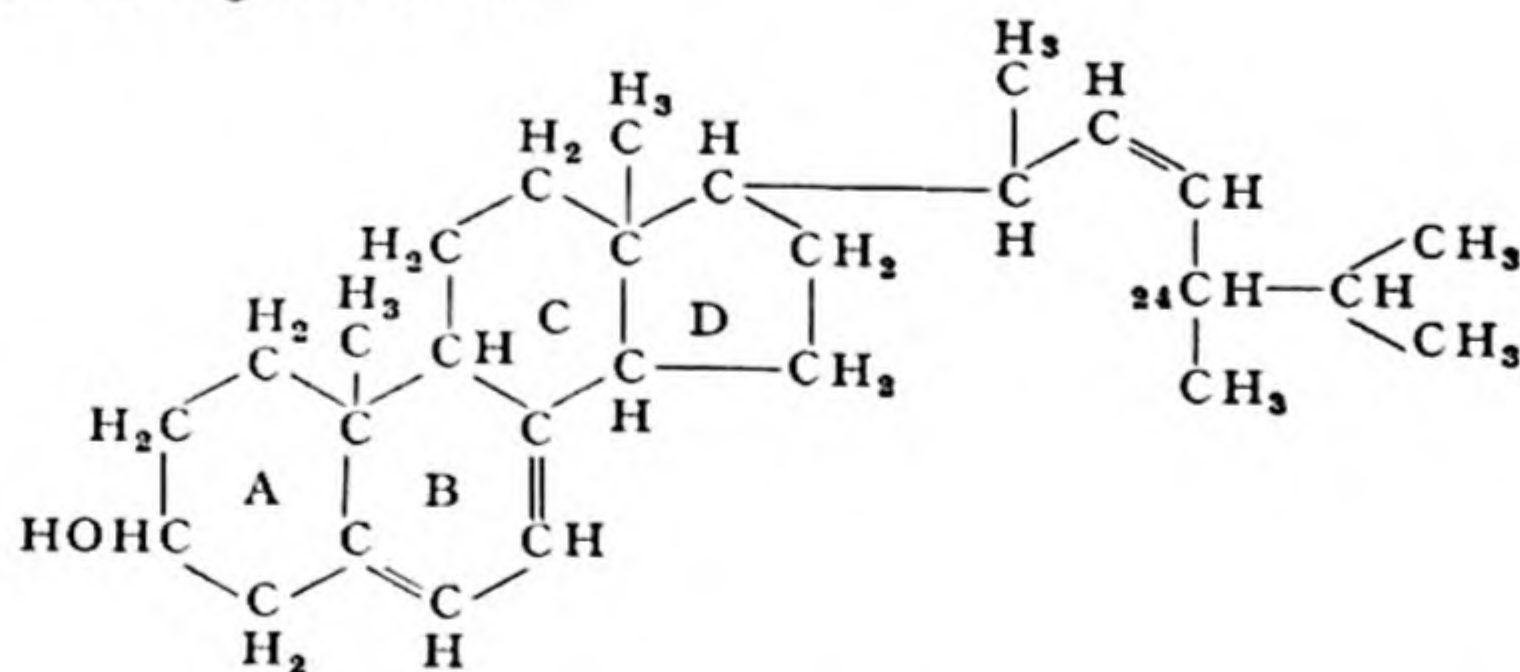
with chromic acid, is acetone; this compound is not found among the oxidation products of either cholic acid or cholanic acid. It is obvious therefore that the extra three carbon atoms, which are present in cholesterol but not in cholic acid, must occur in the former as the group $-\text{HC} \begin{array}{l} \nearrow \text{CH}_3 \\ \searrow \text{CH}_3 \end{array}$. It is in fact

possible to carry out the oxidation of cholestane in such a way that acetone is split off with the production of an acid having the composition $\text{C}_{24}\text{H}_{40}\text{O}_2$; this acid is not, however, identical with cholanic acid. In the oxidation of coprostane, however, along with acetone there is produced an acid $\text{C}_{24}\text{H}_{40}\text{O}_2$ which is identical with cholanic acid. From this it follows that the same ring-skeleton exists in both cholanic and cholic acids as in coprostane and hence also in cholesterol; this observation confirms the conclusion drawn from dehydrogenation with selenium. The structure of the side chain in cholanic acid is deduced from an examination of the products produced by step-wise oxidation; from these investigations it follows that the side chain in cholanic acid, and therefore in cholesterol also, is attached to the carbon atom in a five-ring and that this must be carbon atom 17.

(b) Vitamins of group D

305. *Vitamins of group D* occur in the unsaponifiable portion of cod liver-oil as appears from feeding experiments on rats. Deficiency of the *D*-vitamins causes rachitis. Before vitamin-*D* had been isolated in a pure state, another strongly antirachitically active substance was isolated from the products obtained by irradiating ergosterol with ultra-violet light (BOURDILLON; WINDAUS 1932). This substance, *calciferol* $\text{C}_{28}\text{H}_{44}\text{O}$ or *vitamin-D*₂, m.p. 116° , $[\alpha]_{\text{D}}^{20} = 82.6^\circ$ (in acetone), is isomeric with ergosterol.

The structure of ergosterol is:

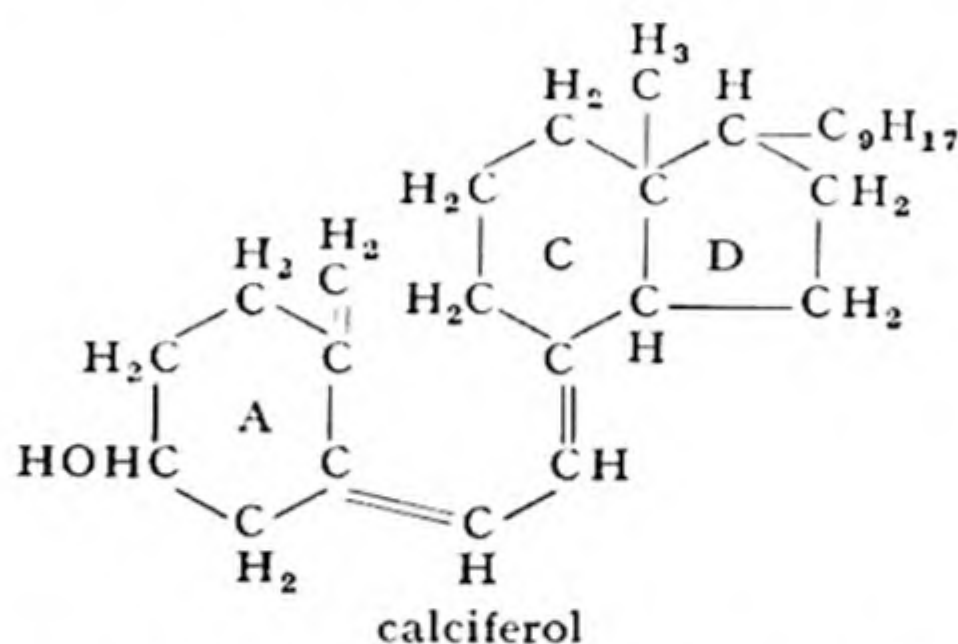


The ring system is the same as that of cholesterol (304) as is shown by the composition of the products obtained on oxidative degradation. Amongst these products 2,3-dimethylbutanal $\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CHO}$ is found, which determines the position of the double



bond and of the methyl group on carbon atom 24 in the side-chain. From the form of the absorption curve of ergosterol in the ultraviolet and from the formation of an addition compound with maleic anhydride (see 291) it follows that the double bonds in ring B are conjugated.

The structure of calciferol (vitamin- D_2) was established by WINDAUS and HEILBRON and their co-workers (1935). In this compound ring B is opened. This follows from the fact that the dihydro-vitamin, in which the side-chain is saturated, gives an addition product with maleic anhydride from which naphthalene is obtained by heating with palladium; dehydrogenation takes place as well as fission of that part of the molecule containing rings C and D, while at the same time, the hydroxyl group in ring A is replaced by hydrogen. In the oxidation of calciferol, formaldehyde is produced from the $=CH_2$ -group and an unsaturated aldehyde $C_{21}H_{34}O$, derived from the part of the molecule containing rings C and D with the side chain:



Vitamin- D_3 was isolated from the liver-oils of the sole and halibut (BROCKMANN); it has a powerful antirachitic action. It has the same side-chain as cholesterol and can be obtained from 7-dehydrocholesterol $C_{27}H_{44}O$, by irradiation with ultra-violet light. It is assumed that this brings about the opening of ring B so that the difference between vitamin- D_3 and calciferol consists in the composition and structure of the side-chain.

(c) Sex hormones

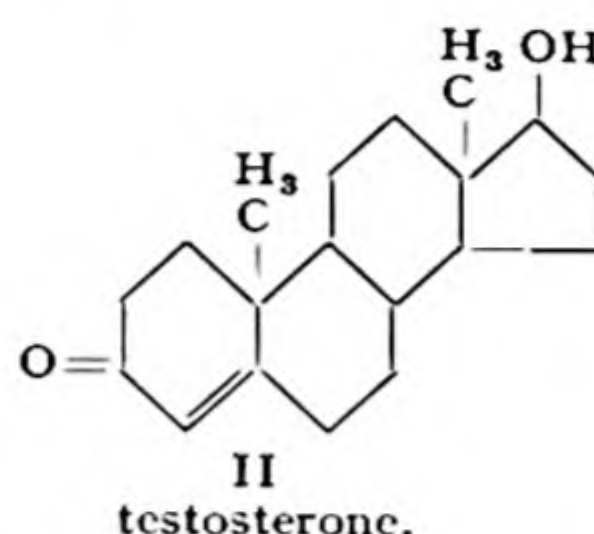
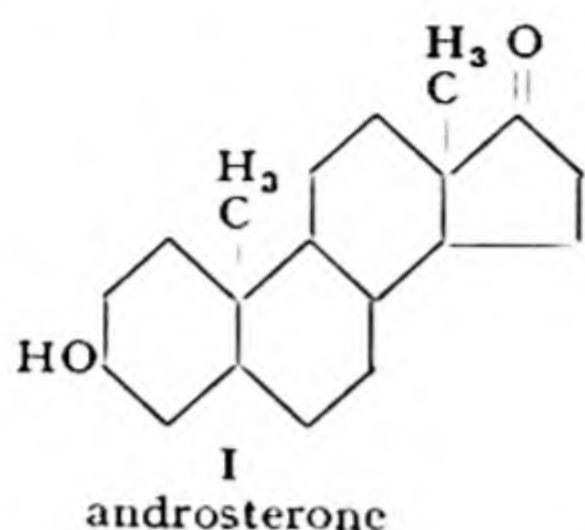
The sex-hormones are discussed in this section because these compounds have the ring system of the sterols.

Male sex-hormones. Very small quantities of hormones occur in the testicles of mammals, which control the development of the male sex organs and secondary sexual characteristics.

Androsterone $C_{19}H_{30}O_2$ occurs in extremely small quantities (about 1 mg. per litre) in men's urine; it was isolated in a crystalline state in 1931 by BUTENANDT.

The method of isolation and purification of androsterone from urine is controlled by tests on animals, *e.g.* the so called *cock's comb test*. In young castrated cocks the comb does not develop; when androsterone is administered to the animal the comb grows. A method based on this fact is used for determining the androsterone content of preparations containing this compound.

Androsterone $C_{19}H_{30}O_2$ (m.p. 178° and $[\alpha]_D = +93^\circ$) has the properties of a saturated hydroxyketone (I). This hormone is also obtained by oxidising the acetate of *epicholesterol*, a stereoisomer of cholesterol (p. 498), with chromic acid, whereby the side chain is split off during the oxidation (RUZICKA):



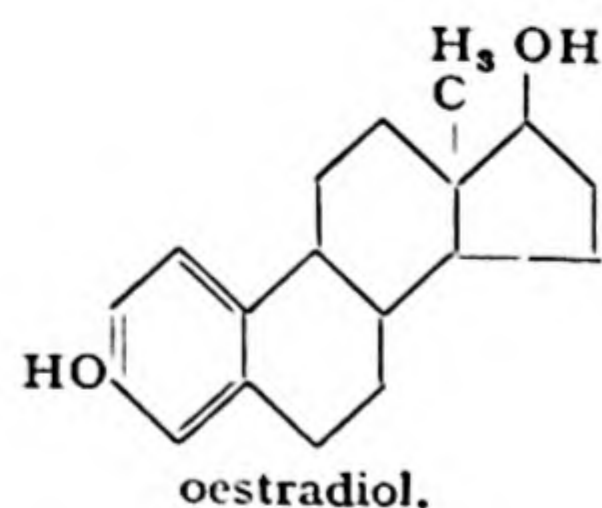
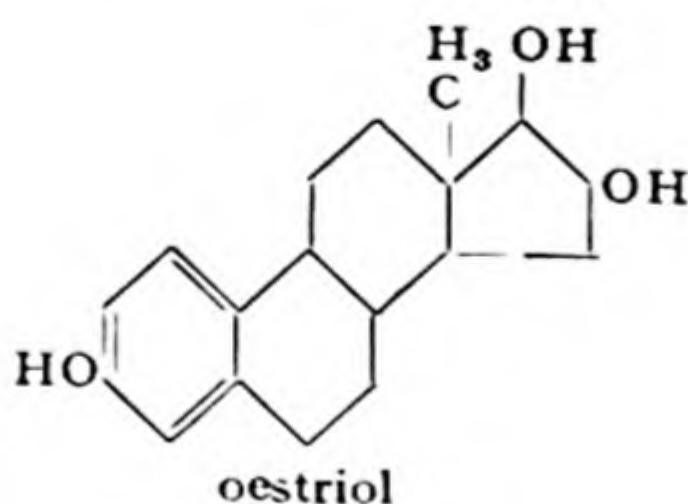
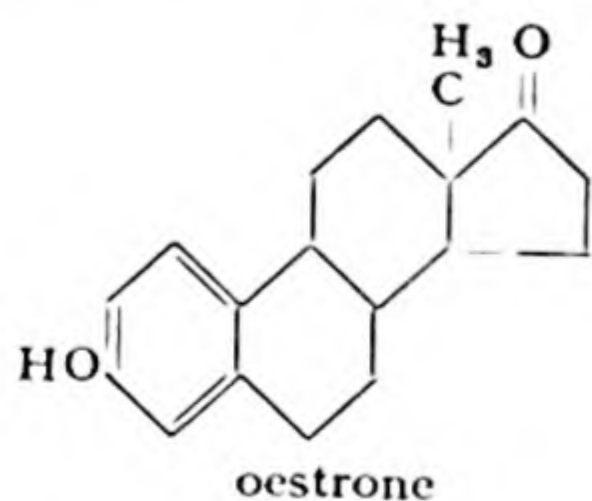
The most potent male sex-hormone, *testosterone*, was isolated from mammalian testicles in 1935 by LAQUEUR and DINGEMANSE; they obtained 10 mg. of this hormone in the crystalline state from 100 kg. of testicular tissue.

Testosterone $C_{19}H_{28}O_2$ melts at 154° and is optically active $[\alpha]_D = 109^\circ$; it may be prepared by a series of reactions from cholesterol.

Oestrone and androsterone occur also in the vegetable kingdom; oestrone has been isolated in the crystalline state from palm kernels.

Female sex-hormones. The ovaries eject substances which regulate the female sexual functions, namely, *follicular hormones* and the hormone from the *corpus luteum*, *progesterone*.

The follicular hormones include the α -*follicle hormone* or oestrone $C_{18}H_{22}O_2$, (m.p. 259° , $[\alpha]_D = +158^\circ$; DOISY, BUTENANDT 1930), *oestriol* or α -*follicle hormone hydrate* $C_{18}H_{24}O_3$ (m.p. 280° , $[\alpha]_D = +30^\circ$; MARRIAN 1930) and *oestradiol* $C_{18}H_{24}O_2$ (m.p. 175°):

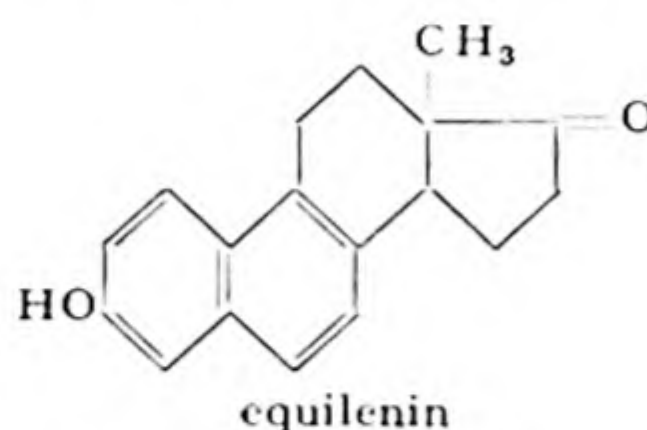
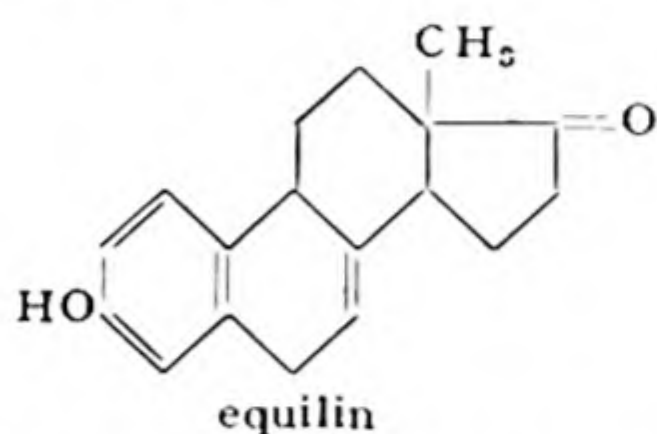


Oestrone, which occurs in the urine of pregnant women, is isolated from the urine of foaling mares. Administration of oestrone to female mammals produces oestrus. It is a remarkable fact that oestrone occurs also in the testis and in the urine of stallions.

Oestriol occurs in the urine of pregnant women; oestradiol occurs along with other follicular hormones in the urine of pregnant mares.

Oestriol splits off a molecule of water when heated with potassium bisulphite and is converted into oestrone. From this it follows that the two hormones have the same carbon skeleton.

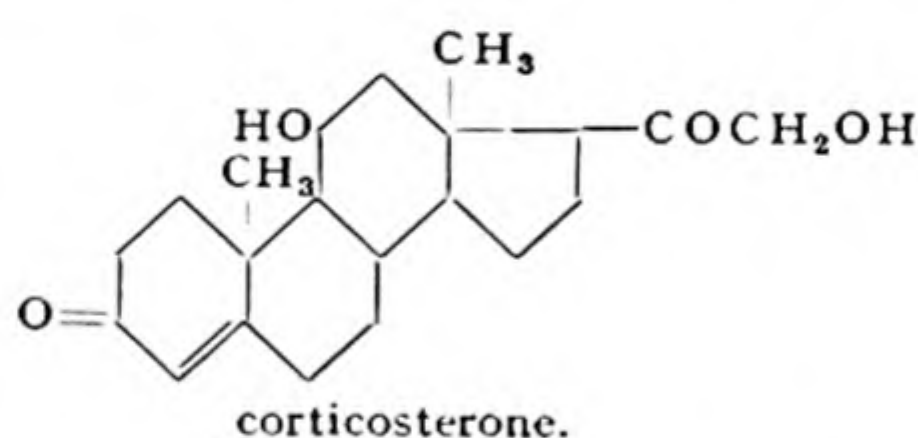
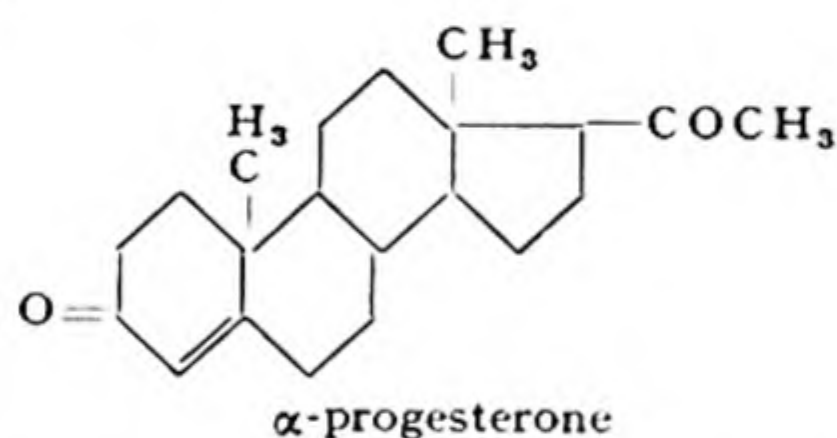
The urine of pregnant mares also contains *equilin* $C_{18}H_{20}O_2$ and *equilenin* $C_{18}H_{18}O_2$. When equilin is heated with palladium, dehydrogenation takes place with the production of equilenin, which contains two aromatic rings. BACHMANN and his collaborators have prepared equilenin synthetically starting from *1-iodo-6-methoxynaphthalene* from which the ring system of tetrahydrocyclopentanophenanthrene is elaborated. *d*-Equilenin was isolated from the synthetic racemate and appeared to be identical with the natural product even as regards physiological action.



Oestrone also has been prepared synthetically (MIESCHER 1948).

The hormone from the corpus luteum, α -progesterone $C_{21}H_{30}O_2$, which can be isolated from the ovaries of pigs, occurs in two modifications melting at 122° and 128° , respectively (dimorphism). It is an unsaturated diketone.

This compound can be prepared by the partial oxidation of stigmasterol (303):



Corticosterone, one of the active hormones from the suprarenal gland is used in medicine in the treatment of Addison's disease. The structure of this substance has been determined in the main by researches carried out by REICHSTEIN.

(iv) VITAMINS AND HORMONES

306. Since the researches of C. EYKMAN and G. GRIJNS (round about 1900) it has been known that a complete diet must contain not only fats, carbohydrates, proteins and mineral constituents but also small quantities of certain organic substances which occur in extremely small quantities in many natural products used for food. At first these compounds could not be isolated in a pure state, so that they could be recognised only by means of their physiological activity by feeding experiments on animals (Mc. COLLUM, OSBORNE and MENDEL, HOPKINS, EVANS, etc.). FUNK was of the

opinion that these substances contained nitrogen and therefore suggested the name *vitamins* (1912). This name has been maintained although it now appears that there are compounds belonging to the group of vitamins which are composed of carbon, hydrogen and oxygen only.

After B. C. P. JANSEN and E. DONATH had isolated vitamin- B_1 or *aneurin* in a pure, crystalline state from rice husks in 1928, the structure of most of the vitamins so far known has been determined by the work of a number of investigators, including WINDAUS, WILLIAMS, KUHN, HEILBRON and KARRER, and a number of these substances have been prepared synthetically.

The vitamins are organic compounds which cannot be built up in the human body, but which are taken up in the food in such small quantities that they cannot be used for providing energy or for building up the material of the cells, yet are essential for the maintenance and normal functioning of the body. The vitamins may be considered as organic catalysts regulating the metabolic processes; in their activity they are comparable with the enzymes. Vitamins are formed in both higher and lower plants (moulds, bacteria).

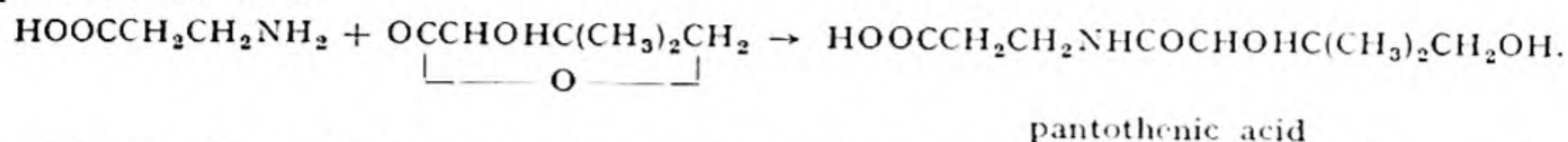
Before the chemical composition of the vitamins had been established, these substances were designated by the letters *A*, *B*, *C*, *D*, etc., and as research progressed further sub-divisions were made, e.g. B_1 , B_2 , etc. The various vitamins are discussed as far as possible in the groups to which they belong by reason of their chemical structure. This section deals with the occurrence and classification of the vitamins.

Two main groups are differentiated, viz. 1, water soluble vitamins, to which belong vitamins of group *B* and vitamin-*C*, and 2, vitamins, which are soluble in fatty oils and to which belong vitamin-*A*, vitamins of group *D* (305), vitamin-*E* (327) and vitamins of group *K* (281).

Vitamin- B_1 *aneurin* or *thiamin* (345) occurs for example in rice-bran, yeast, wheat (especially in the wheat-germ) and in liver; this vitamin protects the organism against beri-beri.

Vitamin- B_2 , *lactoflavin* or *riboflavin* (see 350) occurs in milk-whey, white of egg, yeast, liver, wheat-germs and green vegetables. This vitamin protects the body against pellagra and assists growth. In the above-mentioned materials, along with vitamin- B_2 there occur other vitamins whose physiological activity is comparable with that of $-B_2$, so that these vitamins are usually grouped together with $-B_2$ and referred to as the *B*-complex. It is known with certainty that this complex includes *nicotinic acid* and its *amide* (335) and vitamin- B_6 , *pyridoxin* or *adermin* (336). Nicotinic acid has been known since 1879 but it was only in 1937 that this substance was found to have the action of a vitamin (ELVEHJEM).

Pantothenic acid $C_9H_{17}O_5N$, is included in the vitamin-*B* group; it is soluble in water and assists growth in men and higher animals and is widely distributed in nature. It was discovered by R. J. WILLIAMS, who also established its structure. This compound is a derivative of 2-aminopropionic acid (β -alanin) (195). The latter is allowed to react with the lactone of $\alpha\gamma$ -dihydroxy- $\beta\beta$ -dimethylbutyric acid to produce pantothenic acid:



Vitamin-B₁₂, which occurs in exceptionally small quantities in the liver and protects the body against pernicious anaemia, is a red, crystalline, cobalt compound isolated in 1949.

Vitamin-C or *ascorbic acid* (170) was obtained in the crystalline state in 1932 by SZENT GYORGYI; it occurs in fresh vegetables, lemons and other citrus fruits, Hungarian paprika and in potatoes. Vitamin-C deficiency causes scurvy.

Vitamin-A or *axerophthol* (309) occurs in some fish livers and hence also in liver oils of which it forms part of the unsaponifiable fraction; also in egg yolk and in butter but not in vegetable oils and fats. It assists growth and protects the body against xerophthalmia (desiccation of the cornea).

The vitamins of group D have been discussed in section (305).

Vitamin-E or α -tocopherol ("birth-producing") occurs in wheat-germ, maize, oats, cotton-seed and the oil produced from it and also in some green vegetables. Deficiency of vitamin-*E* causes sterility in experimental animals (for its composition and structure see 327).

Vitamin-K₁ or α -phyloquinone (281) occurs in green vegetables, *e.g.* spinach and stinging nettles. It has an antihaemorrhagic action, *i.e.* prevents bleeding.

307. Hormones. These substances are organic compounds secreted into the blood stream by internal glands. Hormones regulate and bring about certain functions in the body. The sex-hormones and also corticosterone have been discussed in a previous section (305).

Insulin, a hormone secreted by the pancreas, regulates the metabolism of carbohydrates in the human body. It is a protein; it is not yet known which groups in the molecule are responsible for the physiological action. *Adrenalin*, a hormone which occurs in the suprarenal gland has already been discussed in 239.

(v) CAROTENOIDS

308. To this group belong two yellow plant pigments *carotene* and the isomeric *lycopene*; both are highly unsaturated hydrocarbons of the composition $C_{40}H_{56}$.

A number of other plant pigments containing oxygen are related to these hydrocarbons. This group of pigments is known as the *carotenoids* after carotene, which was first isolated from the carrot (*daucus carota*). Since these colouring matters are soluble in fats and occur in both animal and vegetable oils, they are also known as *lipochromes*. These compounds have been examined by many investigators including WILLSTÄTTER, ZECHMEISTER, KUHN and especially by KARRER and his collaborators. About seventy carotinoids are at present known, the majority occurring in the vegetable kingdom and a small number in animals. The chemical constitution of thirty five of these compounds has been completely or partially elucidated.

Lycopene, $C_{40}H_{56}$, the red colouring matter in tomatoes (*lycopersicum esculentum*) occurs also, for example, in rose hips and water melons. It crystallises in brownish violet needles melting at 175° and is optically inactive. On catalytic hydrogenation it takes up thirteen molecules of hydrogen and is converted into a compound $C_{40}H_{82}$; hence the molecule of lycopene is aliphatic in structure and possesses thirteen $>C=C<$ double bonds. On oxidation with ozone, almost two molecules of acetone are found for each molecule of lycopene. On oxidation with chromic acid, six molecules of acetic acid and under other conditions *methylheptenone* $(CH_3)_2C=CH(CH_2)_2COCH_3$, are formed, while succinic acid is produced along with acetic acid when the oxidation is carried out with potassium permanganate. On the basis of these oxidation products lycopene has been assigned structure I given on the next page (P. KARRER).

The carbon chain contains eight isoprene units (denoted by dotted lines) arranged in such a way that two symmetrical halves can be distinguished in the lycopene molecule. As far as chemical constitution is concerned, all the other carotinoids may be regarded as being derived from lycopene.

The *carotenes* are very widely distributed in the vegetable kingdom along with chlorophyll (321) and xanthophyll, in leaves, in many flowers and in fruits. It occurs also in the animal kingdom in fat, milk and blood serum.

Three isomeric carotenes $C_{40}H_{56}$, known respectively as α -, β - and γ -*carotene*, are known. The colouring matter in some plants consists of all these three isomers. They are readily soluble in benzene, chloroform and carbon disulphide but very sparingly soluble in alcohol.

For separating the isomeric carotene and other carotenoids use is made of the method of *chromatographic adsorption*, which was discovered by TSWETT and improved by ZECHMEISTER and others. A solution containing a mixture of colouring matters is allowed to flow slowly and uniformly through a column of a suitable absorbent, such as alumina, calcium carbonate, calcium hydroxide, magnesium oxide, calcium sulphate or various clays. The different colouring matters are adsorbed in different parts of the column so that separate coloured rings or bands are formed lying one below the other. At

the end of the experiment, the various coloured portions of the adsorption column are separated and the adsorbed colouring matter in each section is dissolved in an appropriate solvent. A carotene preparation from carrots is dissolved in a mixture of benzene and light petroleum and the solution is then allowed to flow through a column of active clay. γ -Carotene is adsorbed most firmly and a band of this material separates at the top of the column; β - and α -carotene separate lower down the column. The starting material contains about 85 % of β -carotene, 15 % of α -carotene and only 0.1 % of γ -carotene, all of which can be isolated in this way. The chromatographic adsorption method has also been employed for isolating chlorophyll (321), porphyrins (320) and vitamins (306). When dealing with colourless compounds, in some cases where the compounds show a visible fluorescent colour, the adsorption bands can be made visible by irradiation with ultraviolet light.

β -Carotene $C_{40}H_{56}$, crystallises in dark red leaflets, melts at 184° and is optically inactive. On catalytic reduction (with platinum black) it takes up eleven molecules of hydrogen (ZECHMEISTER); hence it contains eleven $>C=C<$ double bonds. On oxidation of β -carotene with potassium permanganate, four molecules of acetic acid, 1,1-dimethylglutaric acid, 1,1-dimethylsuccinic acid and dimethylmalonic acid are produced. *Geronic acid* is produced on oxidation with ozone; on the basis of these results structure II shown on page 507 is assigned to β -carotene.

According to this structure, β -carotene contains the carbon skeleton of β -ionone (290) twice, joined by a chain of twelve carbon atoms carrying two methyl groups as side-chains. The eleven double bonds are all conjugated. There are no asymmetric carbon atoms in this formula, which is in agreement with the optical inactivity of β -carotene.

α -Carotene crystallises in dark red needles, melts at 187° and is optically active $[\alpha]_D = +380^\circ$. It occurs along with β -carotene in vegetable material, e.g. in palm-oil. The structure of α -carotene differs from that of β -carotene in the positions of the double bonds. At one end of the carbon chain in α -carotene the β -ionone grouping can be recognised and, at the other end, that of α -ionone. This structure follows from the fact that *isogeronic acid* as well as *geronic acid* is found amongst the oxidation products of α -carotene. The α -carotene molecule contains an asymmetrical carbon atom, viz. number 6' in the α -ionone ring (see formula III p. 507).

γ -Carotene crystallises in reddish violet needles, melts at 178° and is optically inactive. Only one cyclic group, namely that of β -ionone, occurs in the molecule of γ -carotene (see formula IV, p. 507).

The carotenes and lycopene are oxidised by atmospheric oxygen (autoxidation); this property is connected with the high degree of unsaturation of these compounds. The carotenoids contain a large number of conjugated double bonds in the molecule and may be regarded as being *polyenes*. The colour of these substances, like the intense red of lycopene and the

orange red colour of the carotenes, is connected with this conjugation of a large number of double bonds. Carotenes, lycopene and the other carotenoids give intense blue colours with concentrated sulphuric acid, with trichloroacetic acid or with arsenic or antimony trichlorides.

Xanthophyll $C_{40}H_{56}O_2$ occurs very widely distributed in the vegetable kingdom; the chloroplasts in leaves contain not only chlorophyll but also xanthophyll and β -carotene. It is soluble in wet methanol and can be separated in this way from β -carotene. Xanthophyll is a dihydroxy-derivative of α -carotene, the hydroxyl groups being in the carbon rings.

Zeaxanthin (more rationally this should be called *zeaxanthol*) $C_{40}H_{56}O_2$, which occurs in maize grains and, as an ester, in other fruits and flowers, is a dihydroxy-derivative of β -carotene.

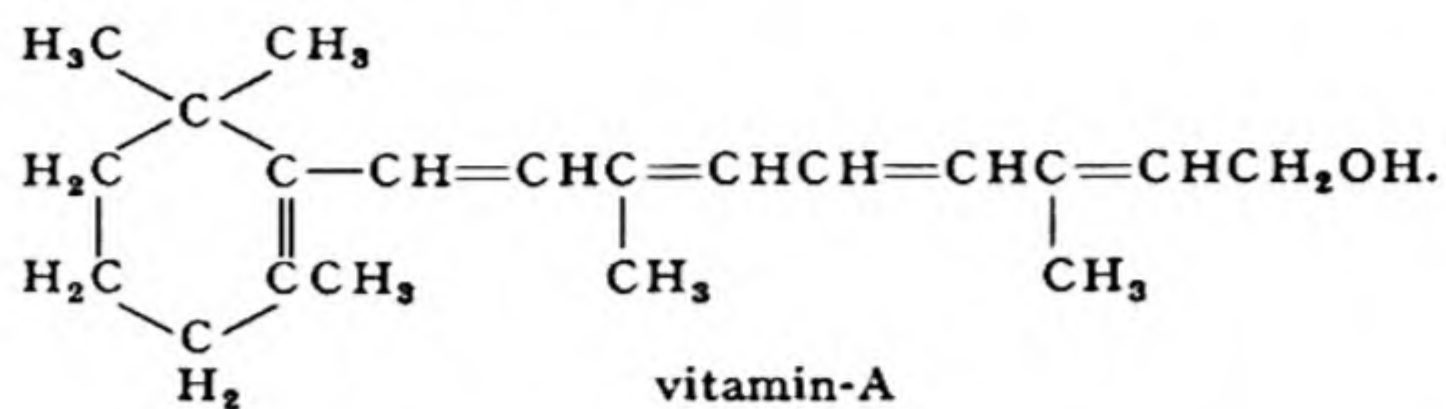
Astacin $C_{40}H_{48}O_4$ (more rationally *astacone*) is a red colouring matter which can be isolated from the shells of crayfish (*astacus*) and other crustacea. It is 3,4,3',4'-tetraketo- β -carotene; the grouping $-\text{CH}_2-\text{CO}-\text{CO}-\text{C}(\text{CH}_3)=$ occurs in both rings.

Crocin, the colouring matter of saffron, is the ester of *crocetin*, $C_{20}H_{24}O_4$, with two molecules of gentiobiose (177). On alkaline hydrolysis it gives crocetin, which was first isolated from crocus flowers. It is a dicarboxylic acid; it forms a dimethyl ester when treated with diazomethane. On catalytic reduction this ester takes up seven molecules of hydrogen; hence crocetin contains seven $>\text{C}=\text{C}<$ bonds. The structure V given on page 507 is deduced from the products obtained when crocetin is oxidised.

309. *Vitamin-A* or *axerophthol*, $C_{20}H_{30}O$, may be isolated from the liver oil of *Stereolepsis ishinagi* and obtained in a pure crystalline state by recrystallisation from organic solvents at low temperatures; it melts at 64° (BAXTER and ROBESON 1942). According to these investigators vitamin-A occurs in fish liver oils in the form of esters. It has been found that the presence of β -carotene in food produces qualitatively the same effect on animals as vitamin-A (H. VON EULER). It appears that β -carotene is converted into vitamin-A in the animal organism. The liver can contain considerable quantities of this vitamin. Thus β -carotene may be considered as being the "provitamin" of vitamin-A.

Structure. This was determined in 1931 by P. KARRER and his co-workers although they did not possess a specimen of the purity mentioned above. Vitamin-A contains an alcoholic hydroxyl group (formation of an acetate). The vitamin can be recovered by hydrolysis of the acetate and other esters. On catalytic hydrogenation five molecules of hydrogen are taken up. On oxidation with ozone geronic acid is produced in such an amount that it is probable that the β -ionone grouping (290) occurs in vitamin-A. KARRER has worked out methods for identifying the grouping
$$\begin{array}{c} =\text{HCC}=\text{C}< \\ | \\ \text{CH}_3 \end{array}$$
 by oxidative degradation. By oxidising the compound with alkaline potassium perman-

ganate, almost two molecules of acetic acid are formed. This work led to the structural formula given below:



Vitamin-A gives a blue colour with antimony chloride in chloroform; this reaction is used for the colorimetric determination of vitamin-A (CARR and PRICE).

Vitamin-A has been synthesised from β -ionone by ARENS and VAN DORP (1947).

PART THREE
HETEROCYCLIC COMPOUNDS

HETEROCYCLIC COMPOUNDS

310. To this class belong those compounds containing ring-systems in which there are present one or more atoms other than carbon (*hetero-atoms*) and those compounds in which such ring-systems are condensed with one or more benzene rings (**211**). In numbering the atoms in the heterocyclic nucleus, the hetero-atom is numbered 1 if only one such atom is present; if more than one is present, oxygen takes precedence over sulphur and likewise, sulphur over nitrogen.

In the following pages we shall discuss, first of all, five-rings in which the hetero-atom is oxygen, sulphur or nitrogen, along with the more important derivatives of these ring-systems. Then we shall discuss five-ring-systems containing two hetero-atoms; then six-rings in which the hetero-atom is oxygen or nitrogen and their derivatives and finally, six-ring-systems containing two hetero-atoms.

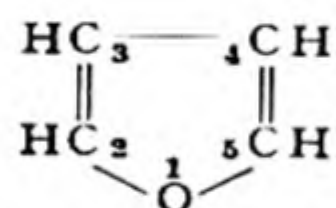
CHAPTER 11

FIVE-RING SYSTEMS WITH ONE HETERO-ATOM IN THE RING

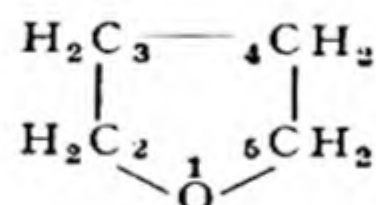
(i) FURAN AND ITS DERIVATIVES

311. *Furan* C_4H_4O , is a colourless liquid smelling like chloroform and boiling at 31.5° ; it may be prepared by heating pyromucic acid (312).

Structure of furan (BAEYER 1877). Furan does not produce hydrogen when treated with sodium and does not react with either hydroxylamine or phenylhydrazine; hence it contains no hydroxyl or carbonyl groups. The oxygen atom must be combined as an epoxy-oxygen atom (111, 160). On catalytic reduction with palladium black at ordinary temperatures, furan takes up four atoms of hydrogen and is converted quantitatively into *tetrahydrofuran*. Two double bonds must therefore be present in the furan molecule. The oxygen atom in tetrahydrofuran also has the properties of an epoxy-oxygen atom, so that the following structures are assigned to these compounds:

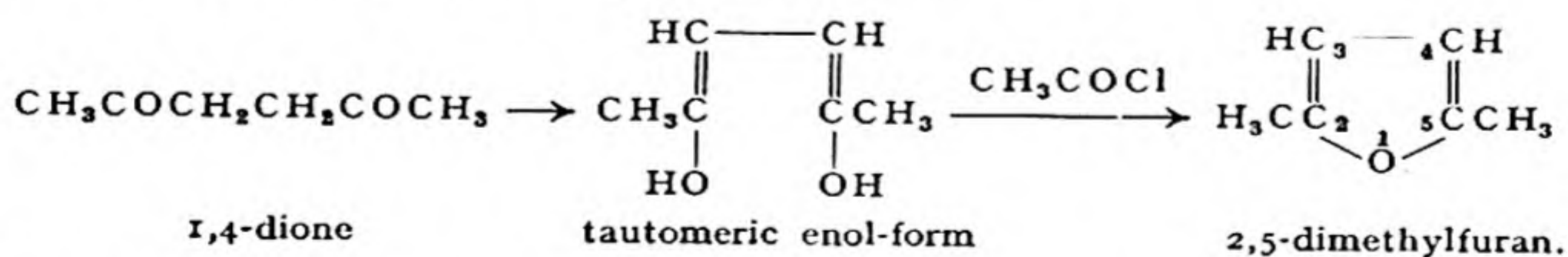


furan



tetrahydrofuran.

This structure is confirmed by the synthesis of furan derivatives from 1,4-diones (146) by treating them with dehydrating agents such as acetyl chloride (PAAL). This process can be explained by supposing that the dione first of all undergoes a tautomeric change and then water is eliminated from the tautomeric compound so produced thus:



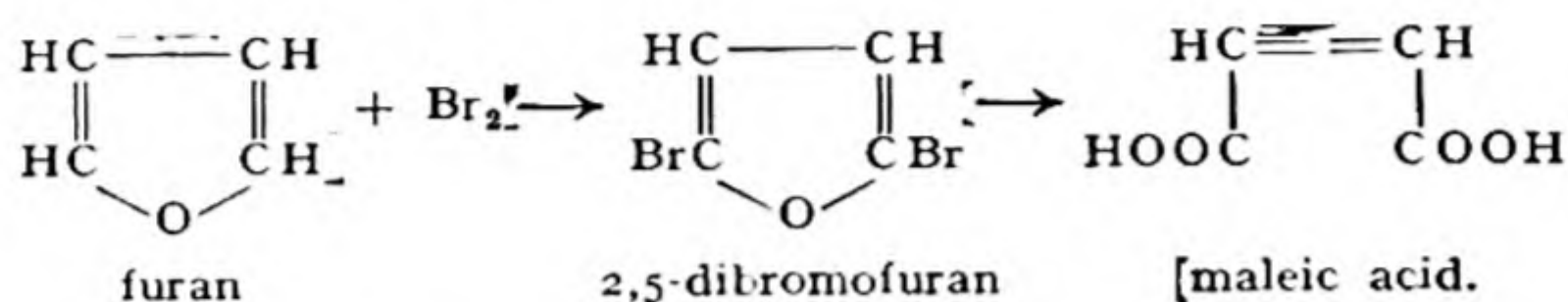
In this way 2,5-disubstituted furan derivatives are produced.

Properties of furan. Under the influence of hydrochloric acid, furan and a number of its derivatives are easily resinified. A reaction characteristic

of furan is the intense green coloration produced on a pine shaving moistened with hydrochloric acid.

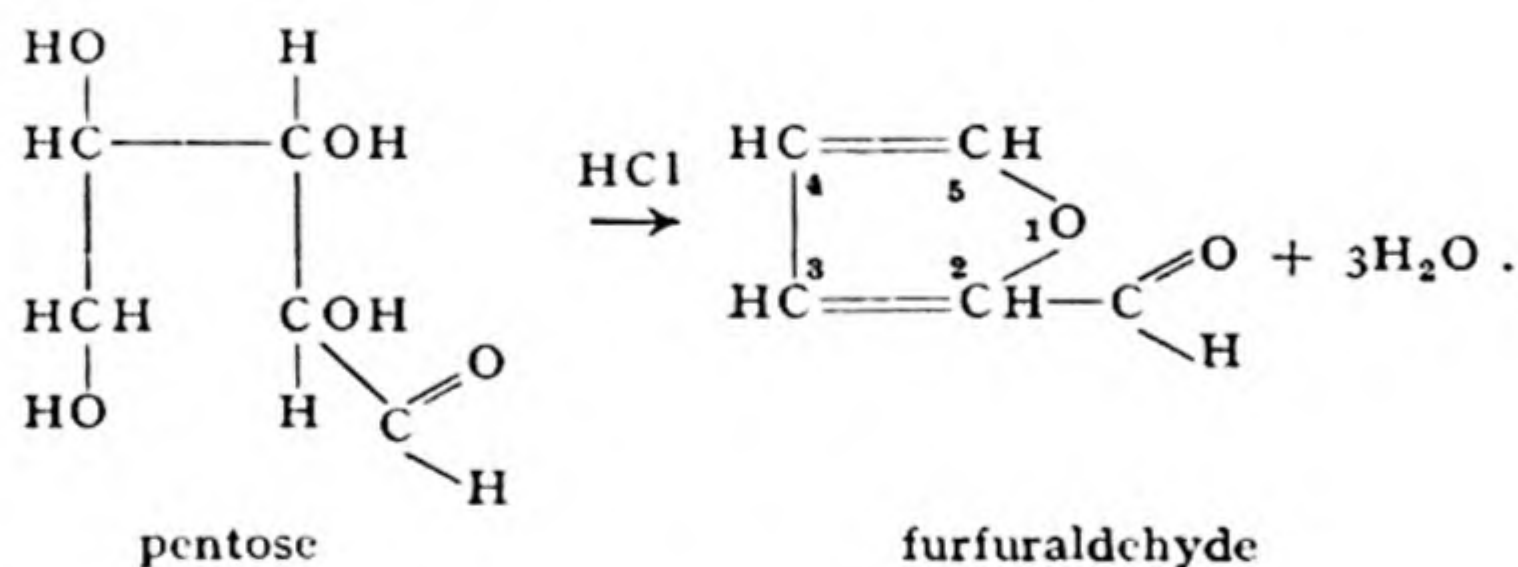
In some substitution reactions, furan shows a similarity to benzene.

Bromine substitutes in the 2- and 5-positions in the furan nucleus. Maleic acid is formed by the oxidation of *2,5-dibromofuran*; this establishes the positions of the bromine atoms:



Furan can be nitrated with nitric acid and acetic anhydride; in this case the nitro-group enters the 2-position, since the nitrofuran obtained is identical with a nitrofuran produced by the action of nitric acid on *pyromucic acid*. In this reaction the COOH-group is replaced by a NO₂-group (RINKES).

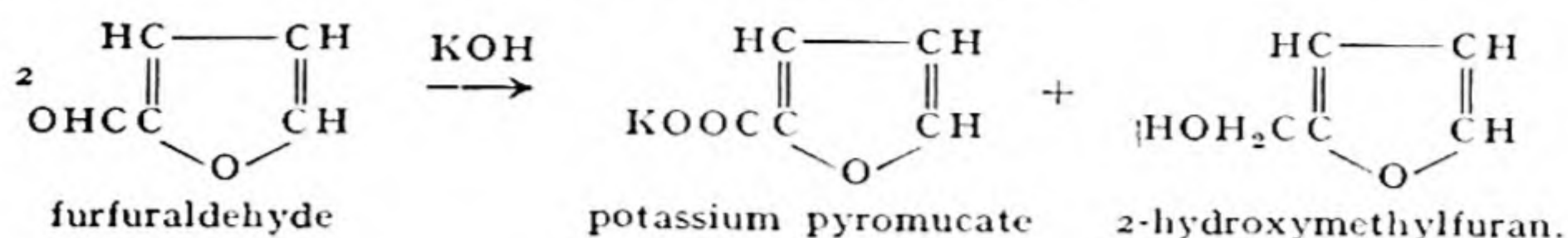
312. *Furfuraldehyde* (furfural or furanal) (C₄H₃O)CHO, is an important derivative of furan. It melts at -35.5° , boils at 162° , has a spec. grav. of 1.1598 at 20° and becomes brown in colour when exposed to air. It is prepared on a technical scale by boiling bran or similar vegetable material containing pentosans (**162**) with dilute hydrochloric acid:



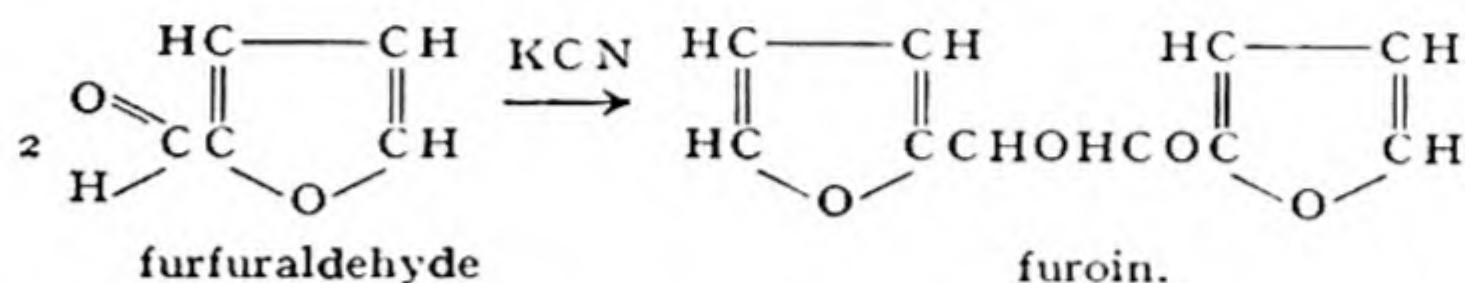
From this method of preparation it follows that the CHO-group is attached to carbon atom 2.

Furfuraldehyde was observed round about 1850 by several investigators on heating bran with dilute sulphuric acid. The name, and also that of furan, is derived from *furfur* = bran.

Furfuraldehyde has the characteristics of an aromatic aldehyde. Like benzaldehyde (**257**) it reacts with alcoholic potash giving an alcohol and an acid (CANNIZZARO reaction), namely, *furfuryl alcohol* or *2-hydroxymethylfuran* and the potassium salt of *furan 2-carboxylic* or *pyromucic acid*:

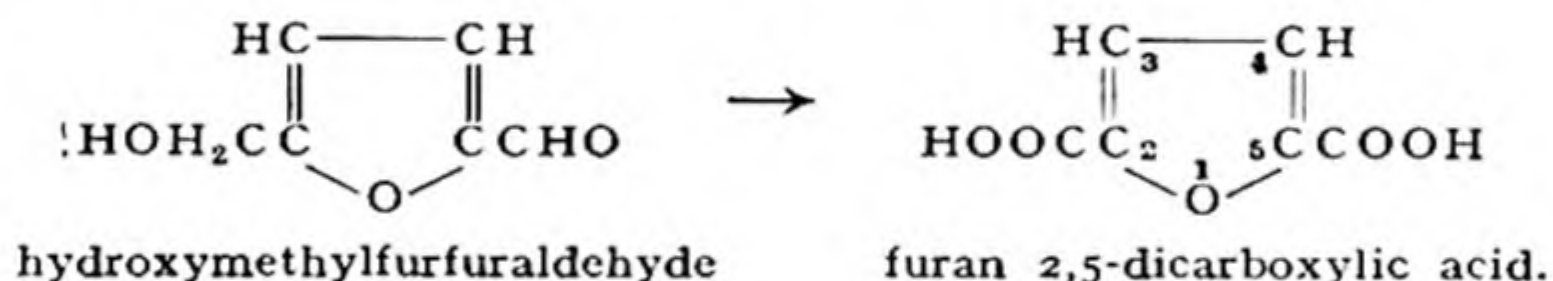


With ammonia, furfuraldehyde forms *hydrofurfuramide* ($\text{C}_5\text{H}_4\text{O}_3\text{N}_2$), which is analogous in composition to hydrobenzamide (257). Under the influence of potassium cyanide furfuraldehyde is converted into *furoin* in the same way as benzaldehyde gives benzoin:



A characteristic reaction for furfuraldehyde is the formation of an intense red colour with aniline and hydrochloric or acetic acid.

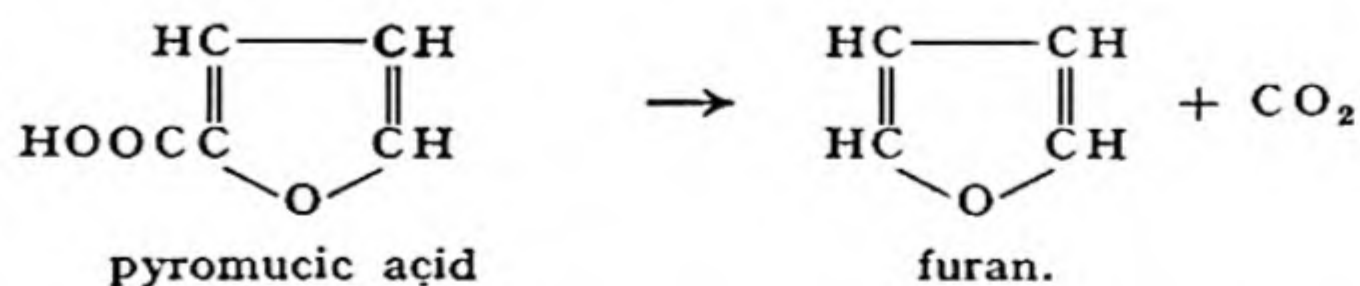
In the same way as furfuraldehyde is obtained from pentoses, *hydroxymethylfurfuraldehyde*, which may be converted into *furan 2,5-dicarboxylic acid* by oxidation, is produced from hexoses, especially ketohexoses, by heating with dilute acids. This method of preparation establishes the structure:



Hydroxymethylfurfuraldehyde on heating with resorcinol and strong hydrochloric acid gives a dark red precipitate. A colour reaction for hexoses and especially for ketohexoses, (SELIWANOFF reaction), is based on this fact.

Furan 2-carboxylic acid or *pyromucic acid* ($\text{C}_4\text{H}_3\text{O}_3\text{COOH}$), melts at 132° , boils at 205° , is readily soluble in hot water and sublimes easily. It is obtained, as the name implies, by the dry distillation of mucic acid (166). It can also be prepared from furfuraldehyde by oxidation with potassium bichromate and sulphuric acid.

On heating to the boiling point, pyromucic acid splits up into carbon dioxide and furan:



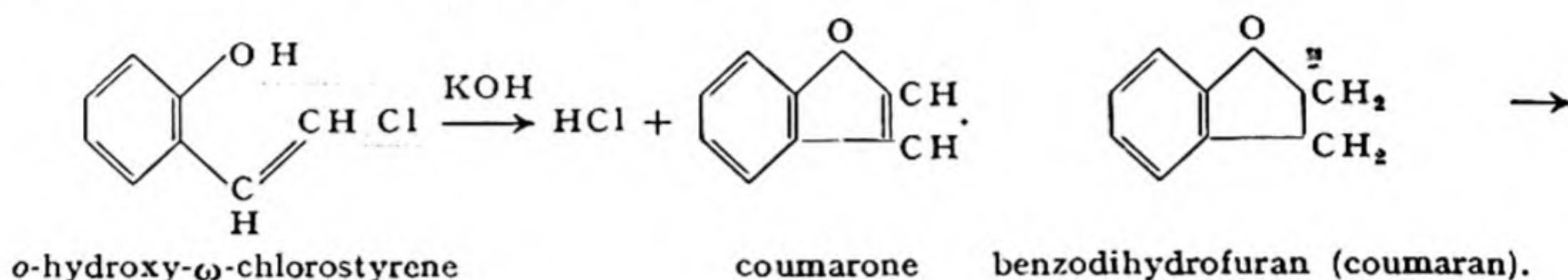
Furan 2-carboxylic acid shows only a few reactions of an aromatic character; it is converted into a sulphonic acid by the action of fuming sulphuric

acid. In most of its properties, however, it resembles an unsaturated fatty acid. It is easily oxidised, rapidly decolorises alkaline potassium permanganate solution and easily adds on four atoms of bromine.

In **160** it is stated that the furan ring-system occurs in the cyclo-acetal form of some saccharides, the so-called furanoid sugars. This nomenclature is not strictly accurate since these compounds are actually derivatives of tetrahydrofuran (**311**).

The *coumaran* or *benzodihydrofuran* ring-system occurs in various natural products.

Coumarone, which occurs in coal-tar, is *benzfuran* and is readily accessible. It boils at 173° and the structure follows from its formation from *o*-hydroxy- ω -chlorostyrene by splitting off a molecule of hydrogen chloride with alkali:

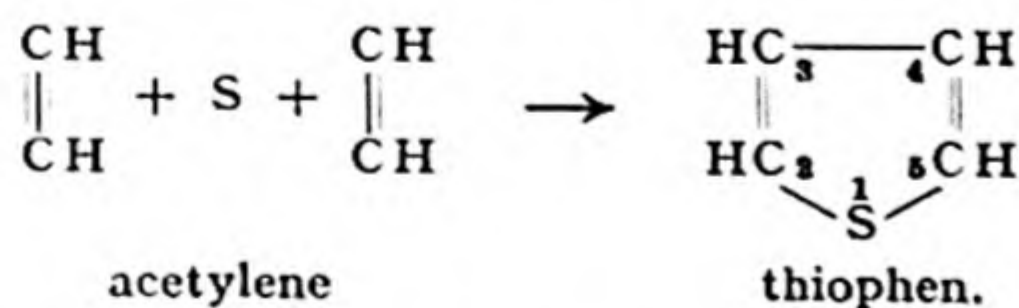


(ii) THIOPHEN AND ITS DERIVATIVES

313. *Thiophen*, $\text{C}_4\text{H}_4\text{S}$, a colourless liquid, b.p. 84° , spec. grav. 1.0664 at 20° , occurs to the extent of 0.5 % in crude benzene obtained from coal-tar (**216**). The homologues, *thiotolen* or *methylthiophen* and *thioxen* or *dimethylthiophen* occur in very small amounts in coal-tar along with toluene and xylene.

Thiophen was isolated by V. MEYER (1883) by shaking crude benzene repeatedly with small quantities of concentrated sulphuric acid until it no longer gave the *indophenin* reaction (a blue colour with isatin **315** in strong sulphuric acid). By this treatment, the thiophen is converted into a sulphonic acid from which it is recovered by heating with water. Benzene and thiophen are more easily separated by boiling the crude benzene fraction with mercuric oxide and acetic acid. *Thiophen dimercurihydroxyacetate* $\text{C}_4\text{H}_2\text{S}(\text{HgO}_2\text{CCH}_3)(\text{HgOH})$, is produced and pure thiophen^r is prepared from this compound by distillation with moderately concentrated hydrochloric acid.

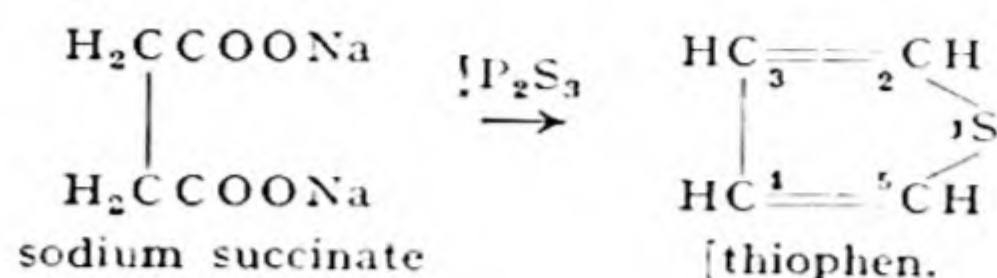
Thiophen can be prepared by passing acetylene over pyrites at 300° . In this reaction a tarry liquid consisting of about 50 % of thiophen is produced:



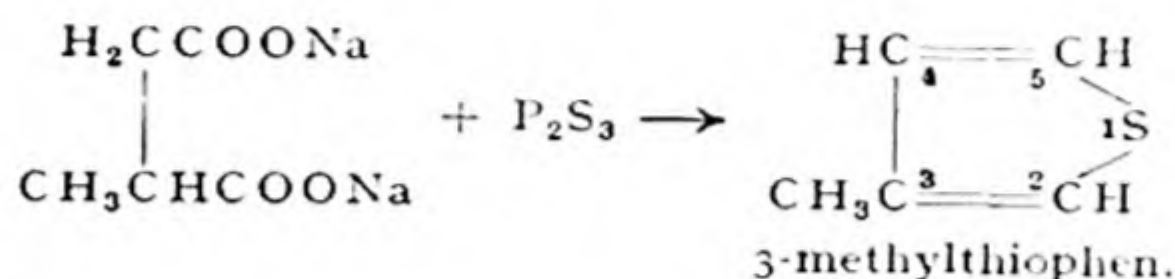
On the basis of this method of preparation and the properties of the substance, the above formula is assigned to thiophen (V. MEYER).

A second method of preparation consists in heating a mixture of sodium succinate and phosphorus trisulphide. A violent reaction takes place with

the evolution of hydrogen sulphide and a liquid consisting principally of thiophen distils over:

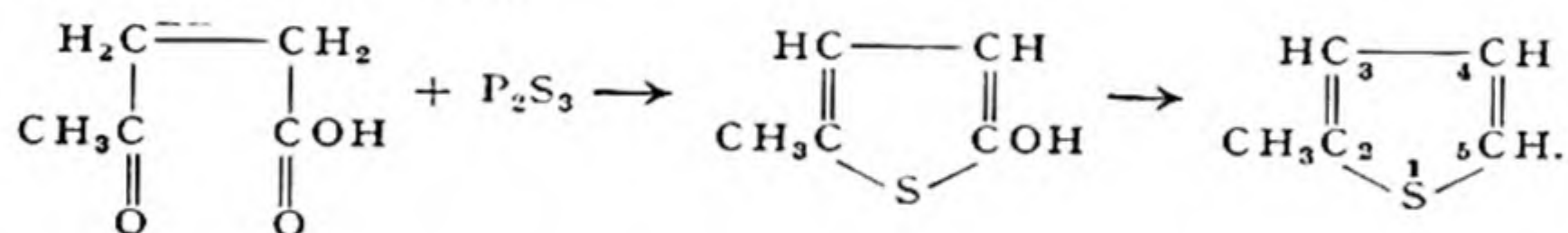


In a similar way *3-methylthiophen* is obtained from sodium methylsuccinate:



and *3,4-dimethylthiophen* from symmetrical dimethylsuccinic acid.

2-Methylthiophen is produced by heating laevulic acid (148) with phosphorus trisulphide. A hydroxy-derivative is formed as an intermediate; the hydroxyl group in this compound is eventually replaced by hydrogen due to the reducing action of P_2S_3 :



2,5-Dimethylthiophen is obtained by warming hexan-2,5-dione with phosphorus trisulphide (compare the analogous formation of 2,5-dimethylfuran on page 513). From this synthesis it also follows that the structure assumed for the thiophen ring is correct.

The known structures of the above-mentioned homologues of thiophen and of the carboxylic acids produced from them by oxidation, serve as a basis for the orientation of thiophen derivatives.

Properties of thiophen and its derivatives. Thiophen is stable towards the oxidising action of potassium permanganate but is oxidised by strong nitric acid.

As a general rule, substitution reactions take place more readily with thiophen than with benzene; the substituent enters position 2.

Halogen derivatives. The hydrogen atoms in thiophen are very easily replaced by the action of chlorine or bromine so that it is very difficult to prepare *mono*-substitution products in this way. The mono-iodothiophen produced by treating thiophen with iodine and mercuric oxide can be converted into 2-methylthiophen by FITTIG's reaction; hence this compound is *2-iodothiophen*. *Thiophensulphonic acids* are produced by the action of cold concentrated sulphuric acid on thiophen.

2-Nitrothiophen is obtained by treating thiophen carefully with a mixture of concentrated nitric acid and acetic anhydride. The same nitrothiophen is produced—along with other nitro-derivatives—by the action of nitric acid on *thiophen 2-carboxylic acid*; in this case the carboxyl group is replaced by a nitro-group (compare the analogous reaction in the nitration of furan 2-carboxylic acid). From this it follows that the nitro-group is situated in the 2-position. 2-Nitrothiophen melts at 46.5° , boils at 225° and has a smell like nitrobenzene.

2-Aminothiophen or *thiophenine* is obtained by reducing 2-nitrothiophen with tin and hydrochloric acid; it is a very unstable compound boiling at 62° at 1 mm. pressure; when exposed to air it is converted into a dark solid mass. The hydrochloride of 2-aminothiophen is more stable than the base.

Aminothiophen cannot be diazotised. It gives an orange coloured aminoazo-compound (249) with benzenediazonium chloride. Thus it has quite different properties from aniline.

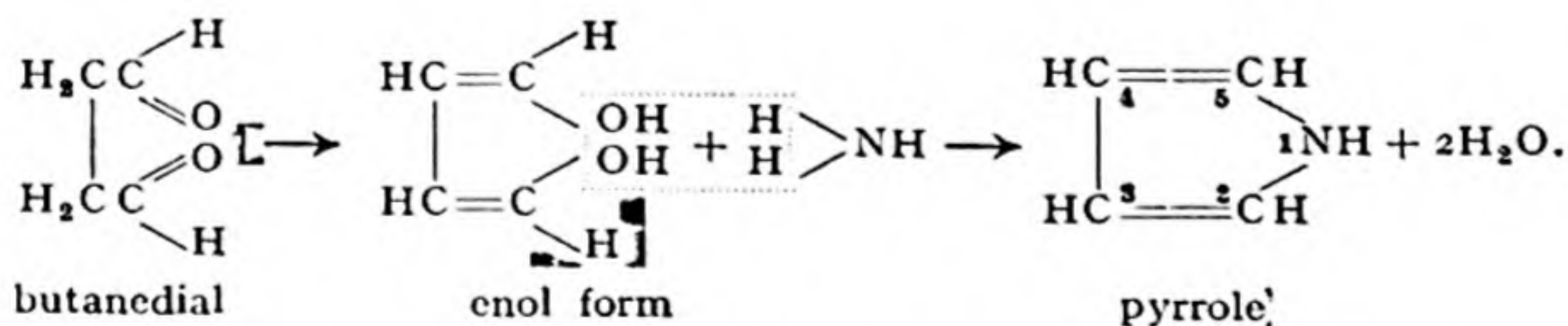
Thienyl ketones are produced by the FRIEDEL-CRAFTS reaction by allowing acid chlorides and aluminium chloride to react with thiophen diluted with ligroin. *2-Acetylthiophen* or *thienyl methyl ketone* obtained in this way, gives thiophen 2-carboxylic acid on oxidation, which establishes its constitution.

(iii) PYRROLE AND ITS DERIVATIVES

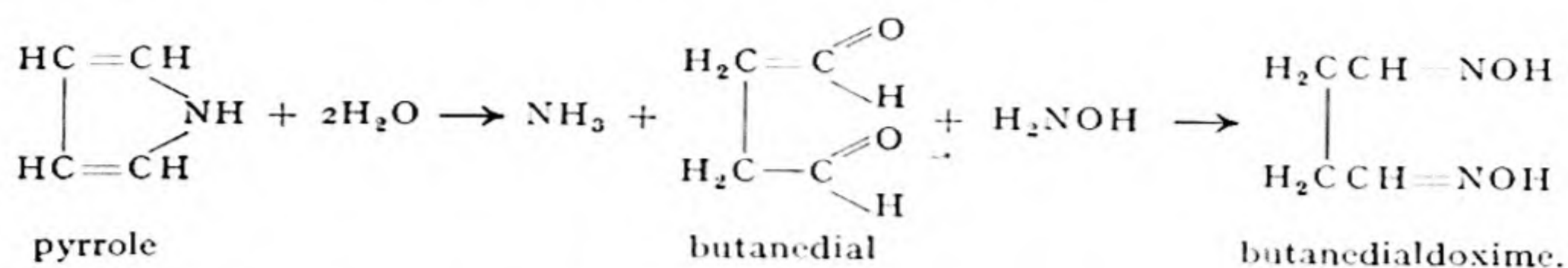
314. Of the five-membered heterocyclic compounds the pyrrole group is the most important.

Pyrrole C_4H_5N , is a colourless liquid, b.p. 131° , spec. grav. 0.948 at 20° , which is immiscible with water; it occurs in DIPPEL's oil. This unpleasant smelling liquid, obtained by distilling bones etc., contains many nitrogenous heterocyclic compounds. Pyrrole can be isolated from the fraction boiling between 120° and 131° (ANDERSON, 1858).

Structure of pyrrole. This can be deduced from the method of preparation from butanedial and ammonia:



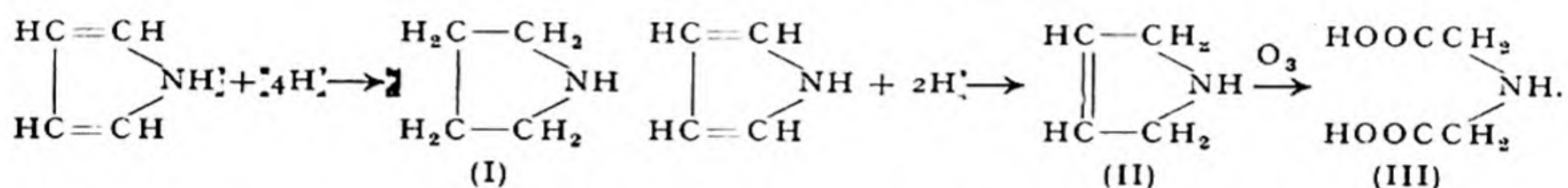
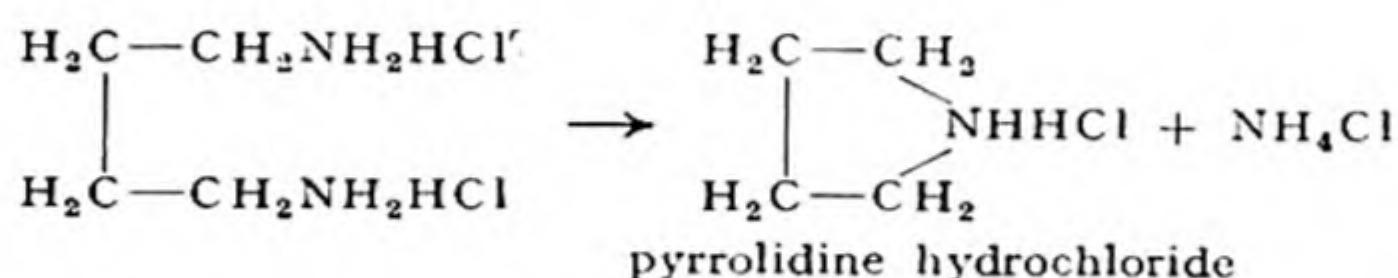
When pyrrole is allowed to react with hydroxylamine in alkaline alcoholic solution, the dioxime of butanedial (succindialdehyde) is produced (CIAMACIAN and SILBER). This reaction may be represented as taking place as follows: a molecule of pyrrole reacts with two molecules of water to form ammonia and butanedial; the latter is converted by hydroxylamine into the dioxime so that pyrrole cannot be re-formed. This reaction is in accordance with the accepted structure of pyrrole:



Opening of the ring system by hydroxylamine occurs also with homologues of pyrrole.

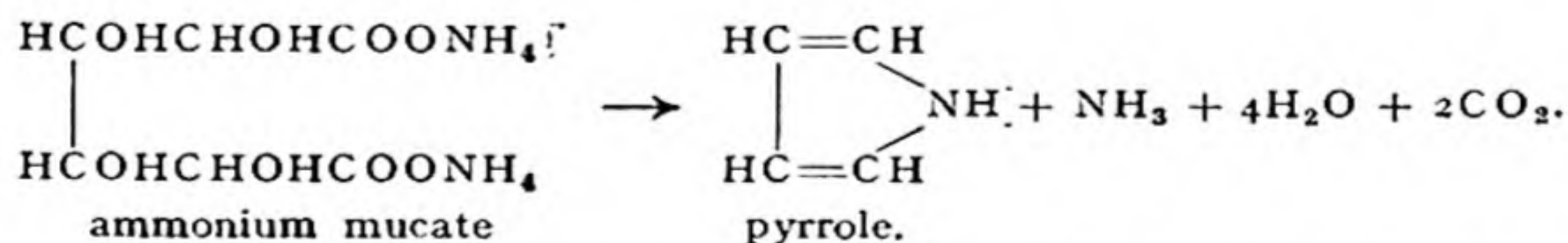
According to the formula given above, pyrrole contains two double bonds; in agreement with this, four atoms of hydrogen are taken up on catalytic hydrogenation in presence of platinum black and pyrrolidine $\text{C}_4\text{H}_8\text{NH}$ (I), a secondary base having the properties of a saturated compound and boiling at 88° , is produced.

Pyrrolidine is also obtained by heating the dihydrochloride of 1,4-diaminobutane:



On reduction with zinc and hydrochloric acid, pyrrole takes up two atoms of hydrogen and is converted into *pyrroline*, $\text{C}_4\text{H}_6\text{NH}$ (II), a secondary base boiling at 91° . Like the partially reduced derivatives of benzene, this base has the properties of an unsaturated compound. The position of the double bond is proved by the formation of iminodiacetic acid (III) on oxidation with ozone (TREIBS).

A practicable method of preparation for pyrrole consists in heating ammonium mucate (166) to $180-270^\circ$ in presence of glycerol as a solvent (SCHWARTZ, 1860):

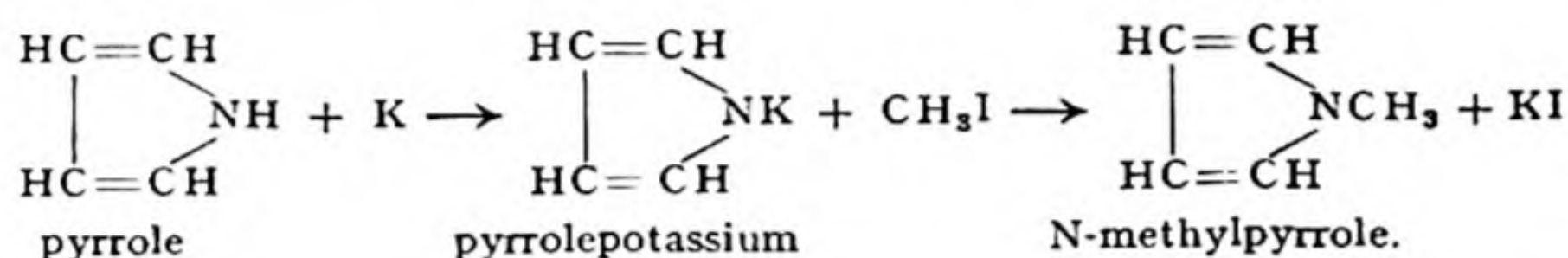


Properties of pyrrole. These were studied round about the end of the last century by CIAMICIAN and his collaborators (DENNSTEDT, SILBER, ANGELI). By the action of strong acids, pyrrole is converted into red-coloured, solid polymers (*pyrrole red*). On this reaction depends a very sensitive and characteristic reaction for pyrrole and its homologues; when a wood shaving

moistened with hydrochloric acid is brought into contact with the vapour of pyrrole or one of its derivatives, it is coloured carmine red.

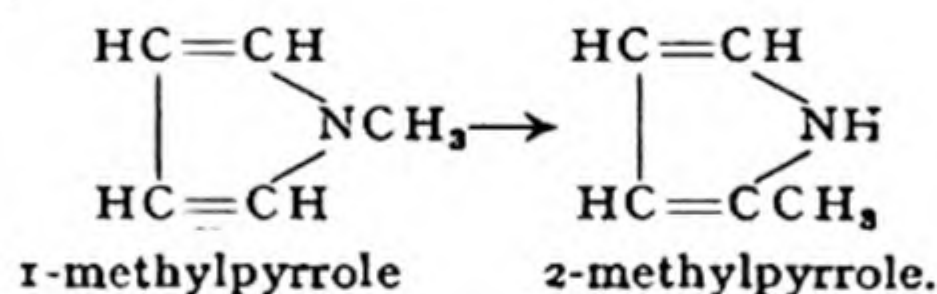
On account of the resinifying action of acids on pyrrole, no salts of this compound are yet known, although it would be expected that a compound having the pyrrole structure would have weakly basic properties.

When pyrrole is boiled with metallic potassium, hydrogen is evolved and a solid substance, *pyrrolepotassium*, C_4H_4NK , in which the potassium is attached to the nitrogen atom, is produced. *Pyrroles alkylated on the nitrogen atom*, e.g. *1-methylpyrrole*, are produced by the action of alkyl iodides on pyrrolepotassium:



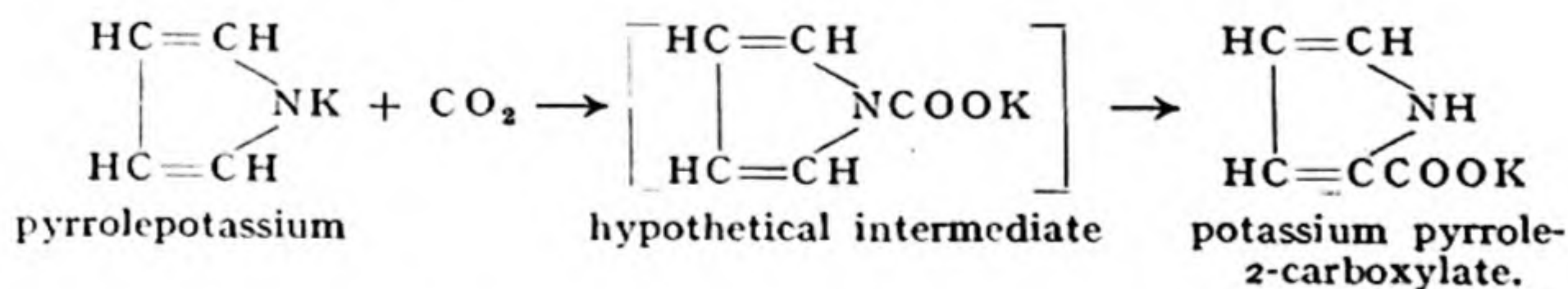
This compound is also produced by heating the methylamine salt of mucic acid. From this it may be concluded that the methyl group is attached to nitrogen.

2-Methylpyrrole. Pyrroles alkylated on the nitrogen atom are converted by heating into pyrroles alkylated on carbon, the alkyl group migrating to carbon atom 2 in all the cases so far studied:



This reaction may be compared with the conversion of methylaniline into toluidines (237).

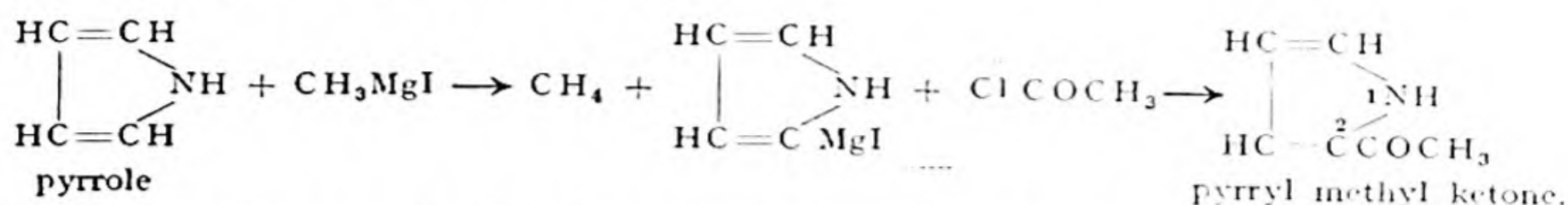
Pyrrole 2-carboxylic acid is produced in the form of its potassium salt by the action of carbon dioxide on pyrrolepotassium:



This reaction is similar to the formation of salicylic acid (263) from sodium phenate and carbon dioxide.

This same pyrrole carboxylic acid is produced in the form of its amide, as a by-product in the preparation of pyrrole from ammonium mucate. From this it follows that the carboxyl group occupies position 2 in this carboxylic acid.

Pyrrylmagnesium iodide is formed by the action of methylmagnesium iodide on pyrrole in ethereal solution, methane being formed in the process (ODDO). This compound can undergo various reactions; thus with acetyl chloride *pyrryl methyl ketone* is produced:



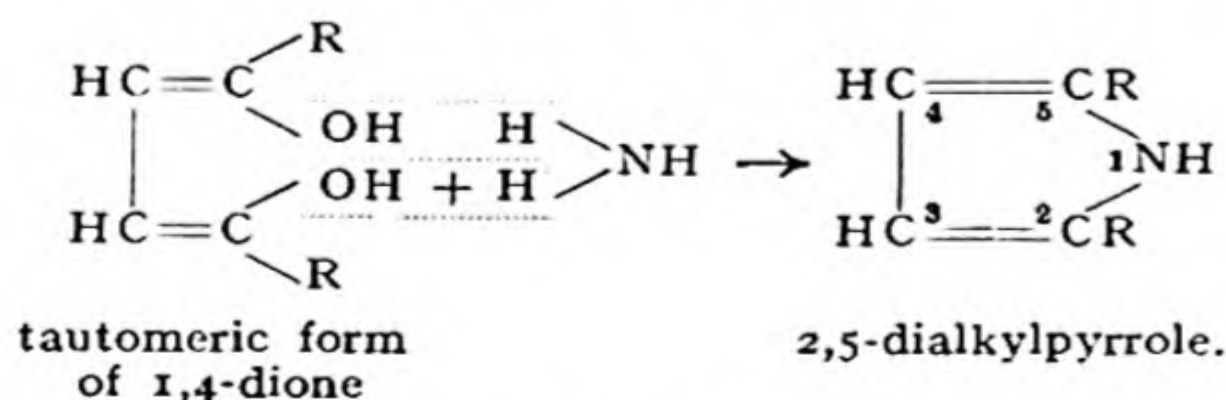
When dry carbon dioxide is allowed to interact with a cold ethereal solution of pyrrylmagnesium bromide, an addition product is formed from which pyrrole 2-carboxylic acid is obtained on the addition of dilute hydrochloric acid. From this it follows that the MgI-group enters the 2-position in the pyrrole nucleus in the ODDO reaction.

In some substitution reactions pyrrole shows a resemblance to aromatic compounds. Halogens do not react by addition but by substitution; mono-, di- and tri-halogeno-substitution products of pyrrole are extremely unstable; the tetra-halogeno-compounds are more stable, especially *tetraiodopyrrole*, $\text{C}_4\text{I}_4\text{NH}$, which is produced by the action of iodine on pyrrole in alkaline medium.

2-Nitropyrrole is obtained by treating pyrrole with concentrated nitric acid in acetic anhydride as the reaction medium (RINKES). That the nitro-group enters the 2-position is clear from the fact that the same nitropyrrole can be obtained by the action of nitric acid on pyrrole 2-carboxylic acid, the carboxyl group being replaced by the nitro-group.

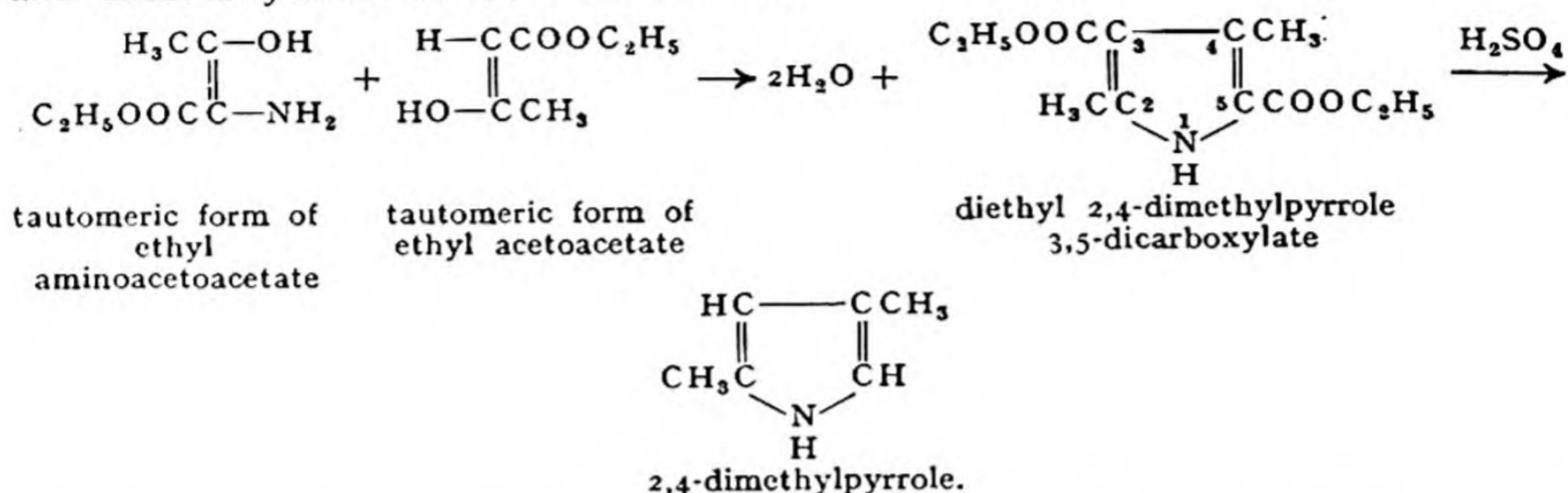
2-Pyrrole-aldehyde (α -pyrrole-aldehyde) is prepared by allowing anhydrous hydrogen cyanide and anhydrous hydrogen chloride to react with pyrrole in ethereal solution. A hydrochloride of an imino-chloride is produced, from which pyrrole-aldehyde is obtained by hydrolysis. In this reaction, pyrrole behaves like a phenol in the synthesis of hydroxyaldehydes by the method of GATTERMAN (258).

Homologues of pyrrole, containing alkyl groups in positions 2 and 5, can be prepared from 1,4-diones (146) and ammonia (PAAL). In this reaction the diones react in the dienolic tautomeric form:

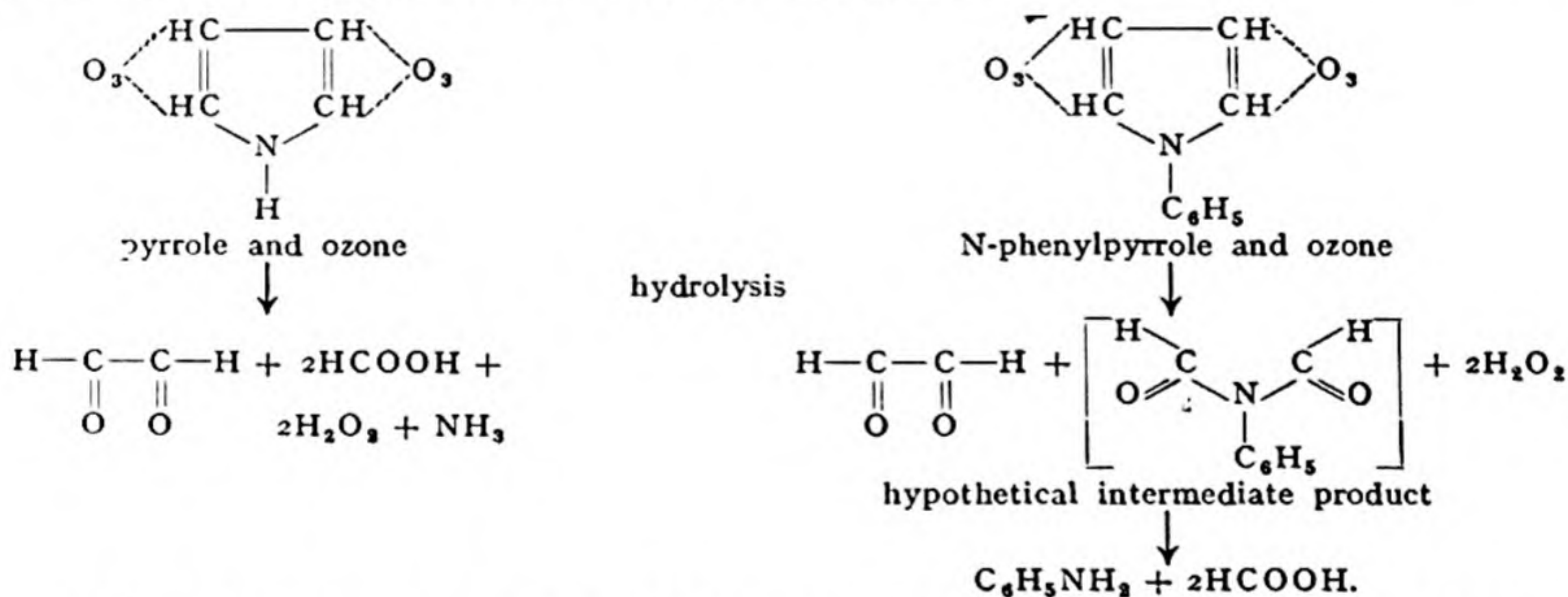


2,4-Dimethylpyrrole is prepared by the KNORR synthesis. Half an equivalent of sodium nitrite and then zinc and acetic acid are added to ethyl acetoacetate and the

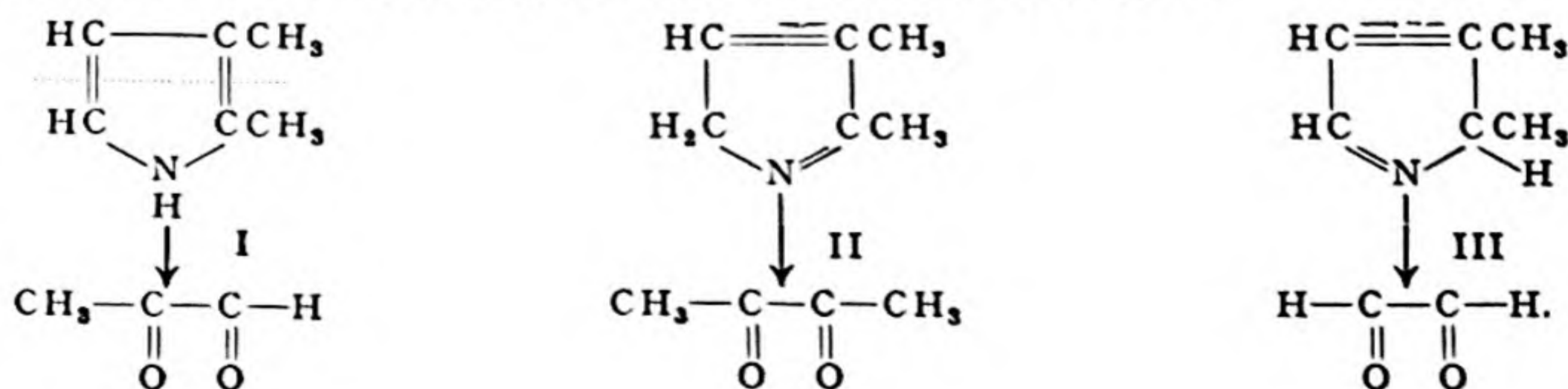
mixture is then warmed. Ethyl nitrosoacetate is formed and converted into ethyl aminoacetoacetate by reduction. Neither of these intermediates is isolated. Ethyl aminoacetoacetate (1 mol.) and ethyl acetoacetate (1 mol.) then react with the elimination of two mols. of water to form *ethyl 2,4-dimethylpyrrole 3,5-dicarboxylate*. The latter is converted into *2,4-dimethylpyrrole* by hydrolysis with dilute sulphuric acid and decarboxylation of the resultant acid:



Tautomerism and mesomerism in pyrrole derivatives. From recent researches of WIBAUT and GULJÉ it has been found that the reaction between pyrrole and ozone and its homologues takes place without appreciable charring if the reaction is carried out at -60° in chloroform as a solvent. In this reaction the double bonds are broken. Glyoxal (145) is produced from pyrrole itself and glyoxal and aniline are obtained in good yields, along with formic acid, from N-phenylpyrrole. These results are in accordance with the classical structural formula for pyrrole:



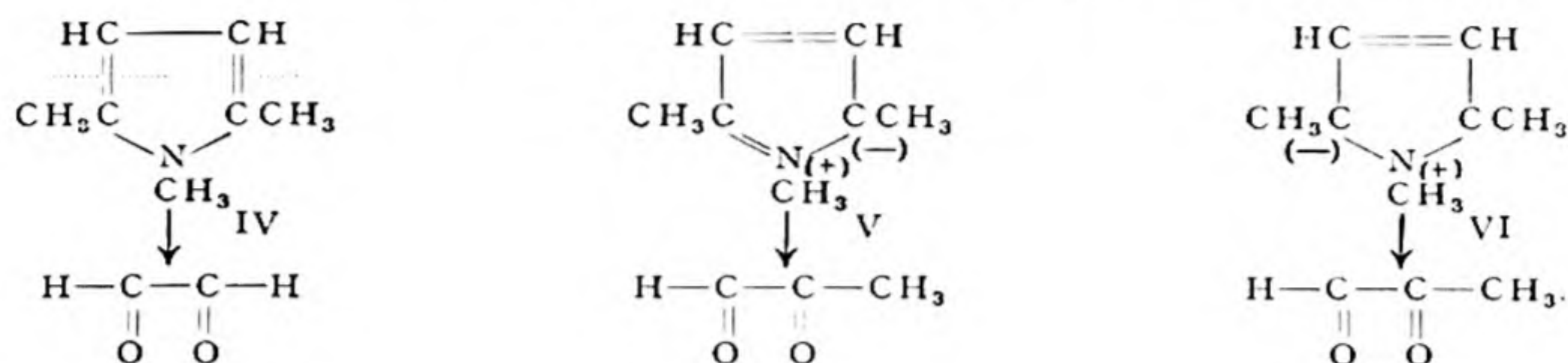
In the degradation of 2,3-dimethylpyrrole with ozone (ozonolysis), dimethylglyoxal, methylglyoxal and glyoxal were obtained, from which it would appear that this compound can react according to three tautomeric structures:



The tautomeric forms II and III can be produced by displacement of the hydrogen atom on the NH-group to one of the carbon atoms 2 or 5, the displacement of the proton being accompanied by a displacement of the double bonds. The occurrence of tautomeric forms is not possible, however, with 1,2,5-trimethylpyrrole IV, since the displacement of a methyl group attached to nitrogen is very improbable.

In the ozonolysis of IV, however, methylglyoxal is obtained as well as glyoxal.

The former substance can be produced if 1,2,5-trimethylpyrrole can react in the mesomeric forms V or VI. In these mesomeric structures the nitrogen atom carries a positive charge and one of the carbon atoms 2 or 5, a negative charge:



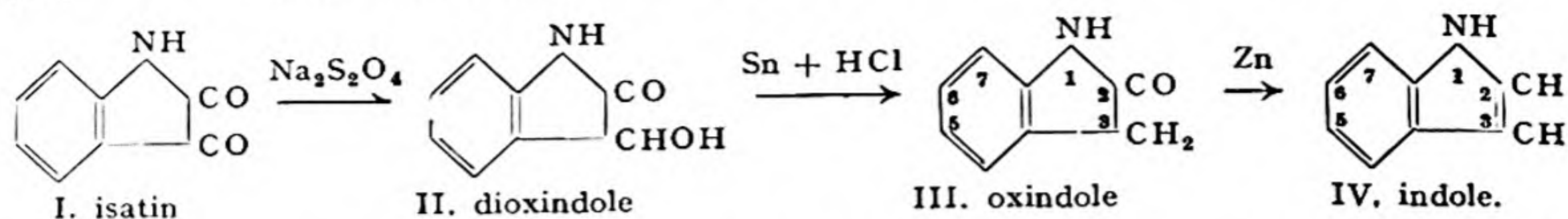
The pyrrole and the pyrrolidine rings occur in a number of compounds of biochemical importance. Pyrrole rings occur in the molecules of the blood pigment and the chlorophylls (see 319, 321). Of the pyrrolidine group, *pyrrolidine 1-carboxylic acid* or *proline* and *hydroxyproline* are of importance because they are degradation products of proteins (see 200). The pyrrolidine nucleus occurs also in a number of alkaloids, viz. in hygrine (354), nicotine (356) and cocaine (358).

Indole or benzopyrrole and its derivatives

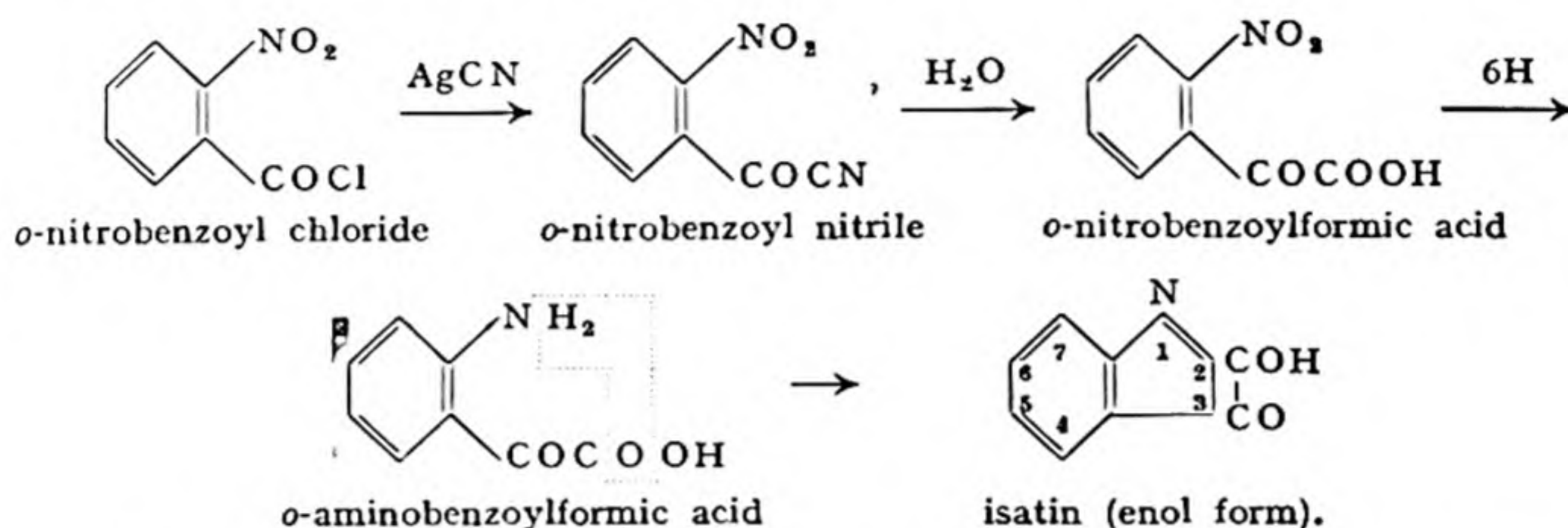
315. *Indole* C_8H_7N , a compound melting at 52° and volatile in steam, occurs in small quantities in coal-tar, in oil of jasmin and in orange blossom. When not quite pure, indole smells very unpleasantly; pure indole, however, finds a use in the perfumery industry on account of its characteristic odour. Indole is important because many of its derivatives occur in natural products.

The potassium derivative of indole, in which the potassium is attached to the nitrogen atom, can be obtained by heating the coal-tar fraction boiling between 240° and 260° with caustic potash.

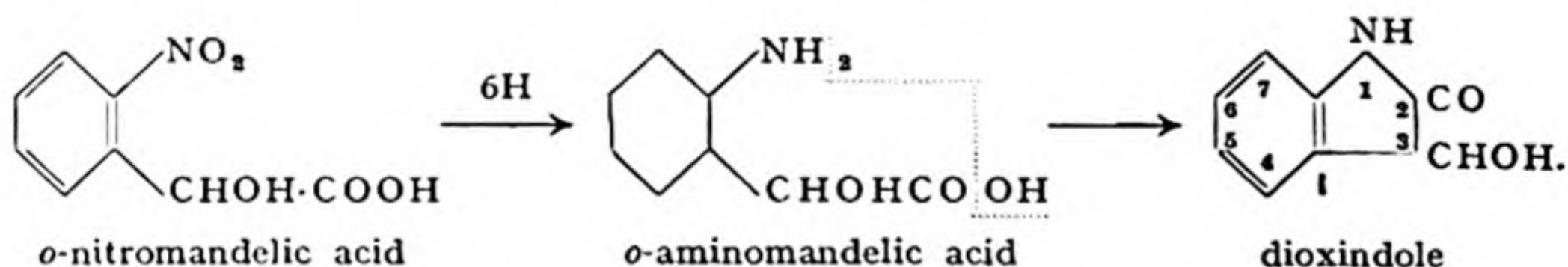
Structure of indole. Indole was first obtained by A. VON BAEYER (1866) in a series of reactions starting from indigo $C_{16}H_{10}O_2N_2$ (316). On oxidising indigo with nitric acid, *isatin* $C_8H_5O_2N$ (I), which melts at 201° (LAURENT, 1841), is formed. On reduction with sodium hydrosulphite, $Na_2S_2O_4$, isatin takes up two atoms of hydrogen and is converted into *dioxindole* $C_8H_7O_2N$ (II), which is converted into *oxindole* C_8H_7ON (III), melting at 127° , by reduction with tin and hydrochloric acid. When oxindole is distilled with zinc dust, *indole* (IV) is produced:



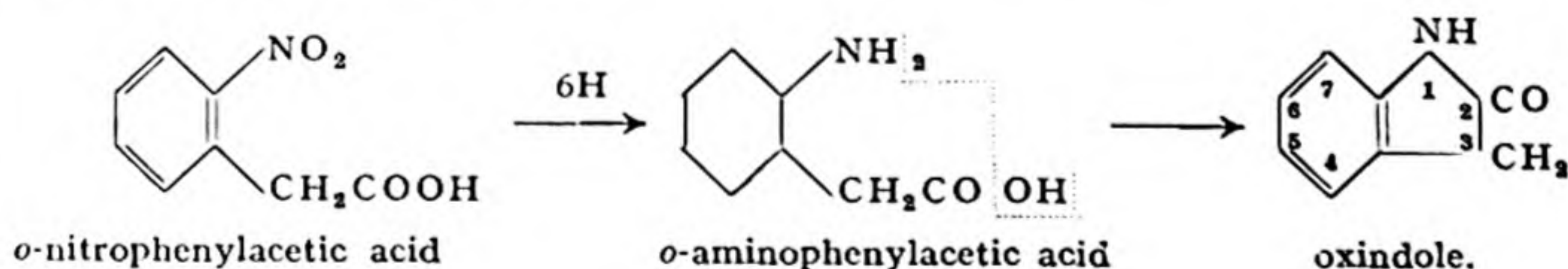
Isatin (I) can be prepared synthetically by treating *o*-nitrobenzoyl chloride with silver cyanide, hydrolysing the resultant nitrile and reducing the *o*-nitrobenzoylformic acid to the corresponding amino-compound (CLAISEN and SHADWELL, 1879). The latter is converted into isatin by the intra-molecular elimination of water:



Dioxindole (II) is produced by the elimination of water from the unstable *o*-aminomandelic acid obtained by reducing *o*-nitromandelic acid:



Oxindole (III) is obtained by reducing *o*-nitrophenylacetic acid and eliminating water from the product:

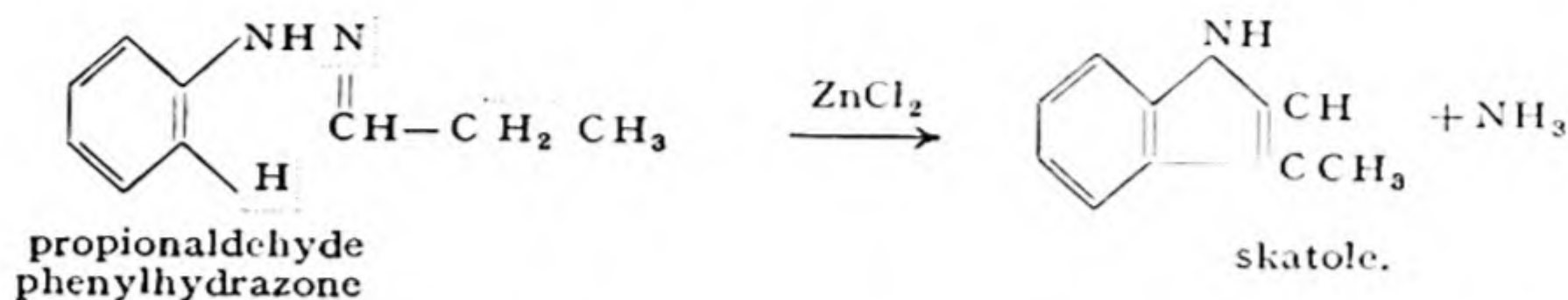


From the above, it follows that indole is built up from a *benzene nucleus* condensed with a *pyrrole ring* (BAEYER, 1870). Its systematic name is *benzopyrrole*.

Properties of indole. It reacts as a feeble base and is coloured red by hydrochloric acid. This reaction is in accordance with the presence of a pyrrole nucleus in the molecule. Indole may be identified as the picrate, which crystallises in bright red needles.

3-Methylindole or *skatole* C_9H_9N , a compound melting at 95° , occurs in faeces and gives the latter its characteristic odour. It is produced by the bacterial decomposition of proteins containing tryptophan as a structural unit or by decomposing them by means of caustic potash.

Homologues of indole can be prepared by the general method devised by E. FISCHER, in which phenylhydrazones of aliphatic aldehydes or ketones are heated with zinc chloride:

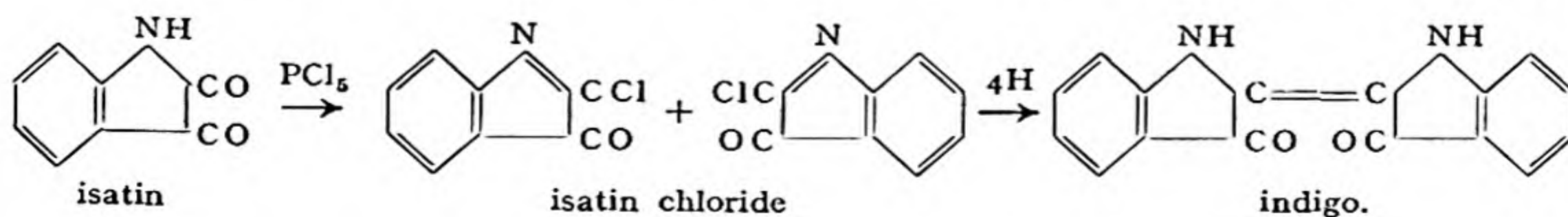


Indoloalanine or tryptophan $C_{11}H_{12}O_2N_2$, m.p. 289° , is an important fission product of proteins (200). Its structure has been confirmed by synthesis and its systematic name is 2-amino-(3'-indolyl)-ethane 1-carboxylic acid.

Indigo and related dyestuffs

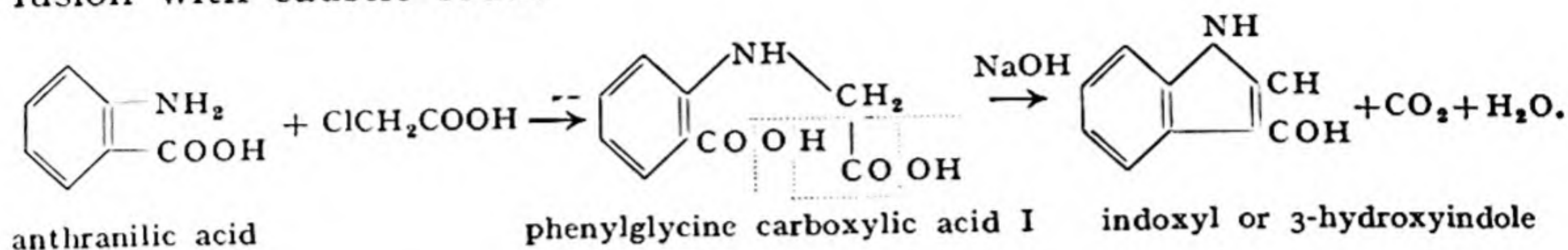
316. Indigo $C_{16}H_{10}O_2N_2$, is one of the most important blue dyestuffs; it is very fast to light and to washing, especially on wool and other animal fibres, and has been known since prehistoric times. A glucoside (179), *indicoside* or *indican* $C_{14}H_{17}O_6N_3H_2O$ (HAZEWINKEL, HOOGEWERFF, TER MEULEN, 1900) occurs in the leaves of certain plants *e.g.* in *indigofera tinctoria* and in *leptostycha*. The indicoside can be recovered from the leaves by extraction with hot water. Besides indican, the leaves also contain an enzyme (208), *indimulsase*, which is rendered inactive, like all enzymes, by boiling water. If the leaves are extraced with cold water, both the indicoside and the indimulsase pass into solution; the glucoside is then split by the enzyme into glucose and *indoxyl*, a yellow crystalline compound, m.p. 85° , which is stable in weakly acid solution but is readily oxidised by atmospheric oxygen in weakly alkaline solution to indigo.

Structure of indigo. It has already been mentioned in 315 that isatin, which contains eight carbon atoms and one nitrogen atom, is produced by the oxidation of indigo. This is exactly half the number of carbon atoms and nitrogen atoms in the indigo molecule. By the action of phosphorus pentachloride on isatin there is produced *isatin chloride*, which may be converted into indigo by treatment with zinc dust and acetic acid (BAEYER, 1870):

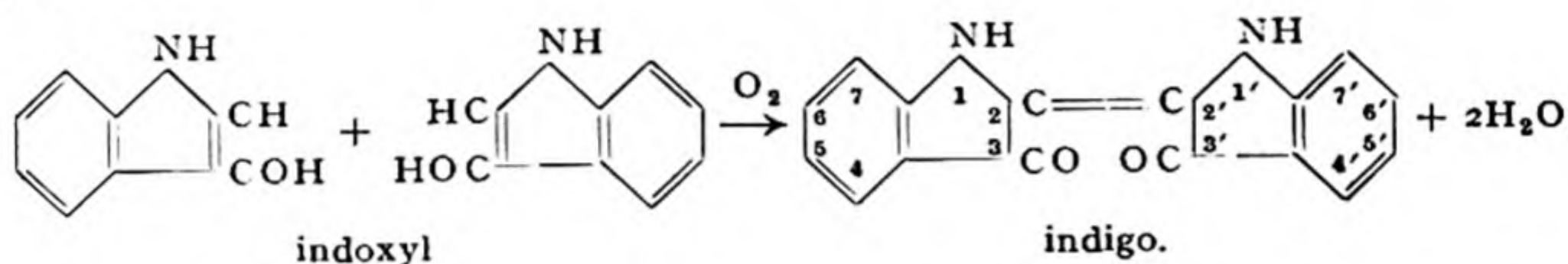


The structure of indigo has been confirmed by several other syntheses devised by BAEYER.

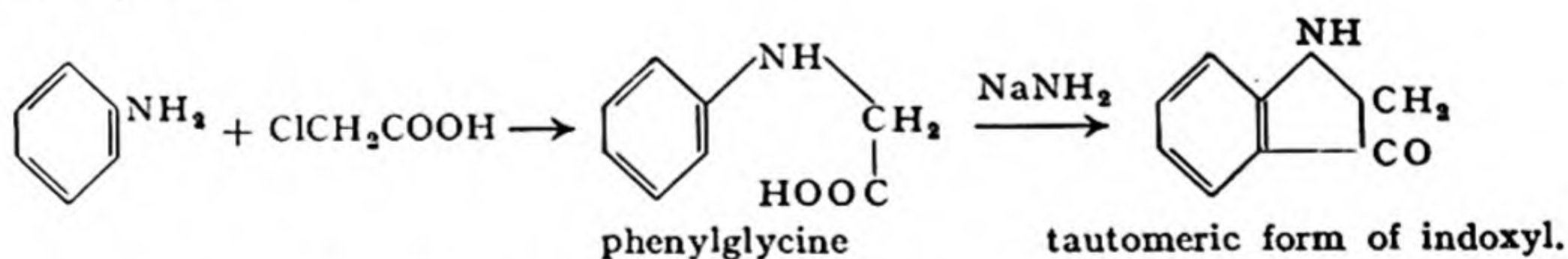
Technical preparation of indigo. The oldest method is based on the HEUMANN synthesis (1890). Anthranilic acid or *o*-aminobenzoic acid (262) is heated with mono-chloroacetic acid to form *phenylglycine carboxylic acid* (I) which is converted into *indoxyl* or 3-hydroxyindole C_8H_7ON , by fusion with caustic soda:



In alkaline solution indoxyl is readily oxidised by atmospheric oxygen to indigo:

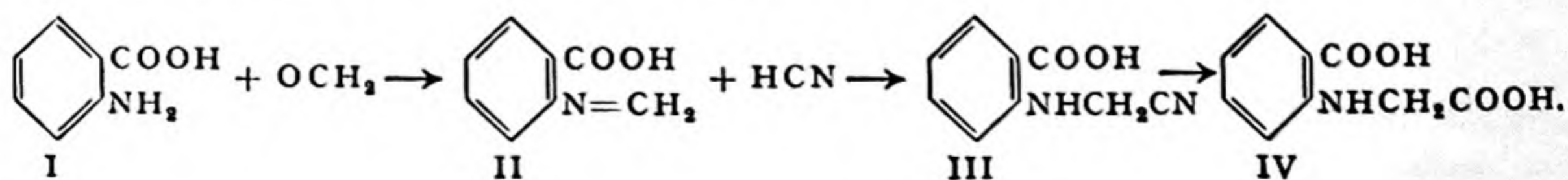


This original method was later superseded by a simpler method, also devised by HEUMANN and therefore generally known as his second synthesis, in which the starting point is aniline. The latter is first of all converted into phenylglycine by treatment with chloroacetic acid, or more recently, by interaction with formaldehyde bisulphite and sodium cyanide to produce *phenylglycine nitrile*, which is subsequently hydrolysed, and the phenylglycine is converted into indoxyl by fusion with caustic soda and sodamide (PFLEGER 1900):

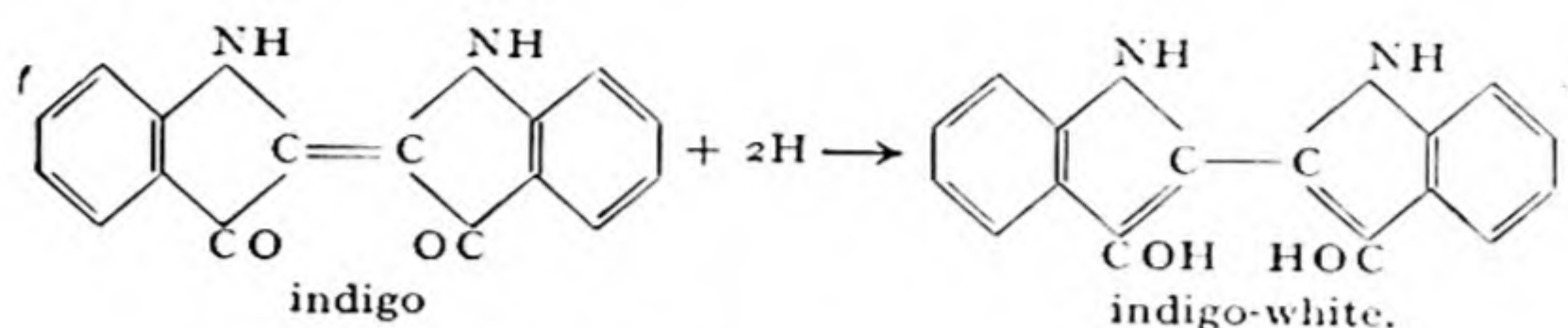


Synthetic indigo has displaced the natural product almost completely.

Finally, indigo can be prepared by heating anthranilic acid (I), formaldehyde and potassium cyanide solution to give, via *methyleneanthranilic acid* (II), *carboxyphenylglycine nitrile* (III) which gives *o*-carboxyphenylglycine (IV) on hydrolysis; the latter is then converted into indigo as already described above:



Indigo-white or *leucoindigo* $C_{16}H_{12}O_2N_2$, is produced by reducing indigo, two atoms of hydrogen being taken up to convert the two carbonyl groups into two $>COH$ -groups:



Indigo-white is soluble in alkalis in accordance with the phenolic character of the compound. The alkaline solution is oxidised by atmospheric oxygen giving indigo in a very finely divided form.

Indigo is reduced to leucoindigo or indigo-white by reducing agents like sodium hydrosulphite, $Na_2S_2O_4$, or "Formosul"; cotton or wool fabrics to be dyed are steeped in such an alkaline solution and then exposed to air when indigo is produced inside the textile fibres.

In the dyeing trade such a dyebath is known as an *indigo vat*.

Reduction with calcium hydrosulphite has the advantage that reduction goes no farther than the leuco-dyestuff stage, so that when it is used no indigo is lost.

Indigo is a *vat dyestuff*, i.e. it belongs to that class of dyestuffs consisting of insoluble pigments, which are converted by alkaline reducing agents into soluble compounds, so called *leuco-compounds*, having the property of being absorbed from solution by vegetable and animal fibres. The leuco-compound is said to have affinity for the textile material. On subsequent oxidation, the insoluble pigment is re-formed on or, more precisely, inside the fibre, which is thereby dyed. The vat dyes have the advantages of being very fast to washing and usually also to light, the fabric requires no pre-treatment like mordanting (252) and, in the case of indigo, the preparation of the vat and the dyeing can be carried out at ordinary temperatures but this is not the case with all vat dyes. There are two main classes of vat dyes, those derived from anthraquinone (282) and other polycyclic quinones and those related to indigo. The latter are known collectively as the *indigoids*; they all contain the grouping $O=\text{C}-\text{C}=\text{C}-\text{C}=\text{O}$, which is the chromophoric group of this class of dyestuffs.

6,6'-Dibromoindigo or the *purple of the ancients*, is a derivative of indigo in which the hydrogen atoms in positions 6 and 6' are replaced by bromine atoms. This was used in ancient times for dyeing expensive cloths; it was obtained from the mollusc *murex brandaris*, which secretes a colourless compound from which the purple separates on exposure to light. FRIEDLÄNDER isolated this compound from this source and established its structure.

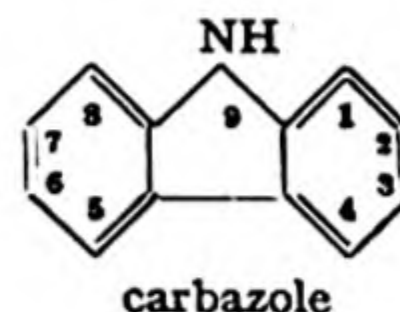
Thioindigo contains sulphur atoms in place of the two NH-groups and is a red dyestuff (FRIEDLÄNDER).

By introducing other substituents, it is possible to obtain various shades of colour so that the group of indigoid dyestuffs is very extensive.

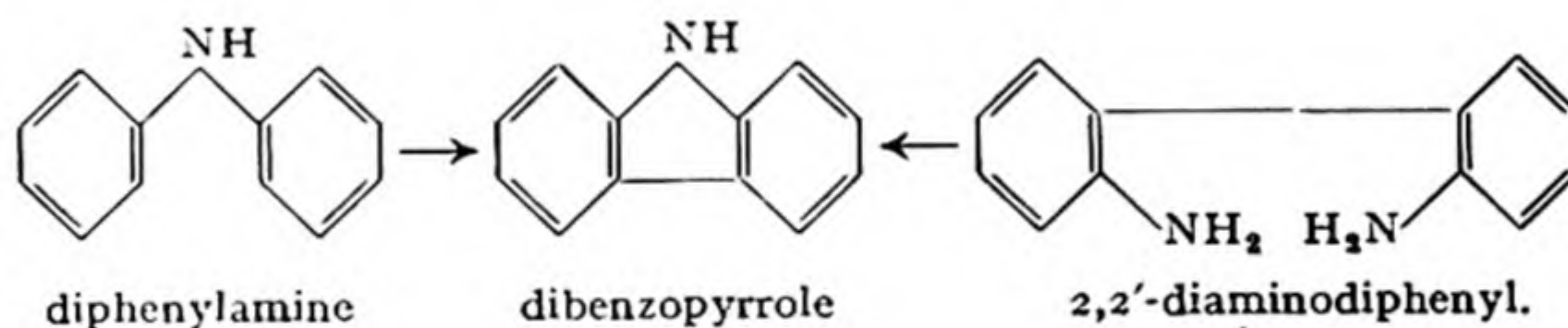
Carbazole or dibenzopyrrole

317. The carbazole molecule consists of a pyrrole ring to which two benzene rings are condensed in *ortho*-positions

Carbazole $C_{12}H_9N$, which was discovered by GRAEBE in 1872 in crude anthracene oil from coal-tar, was so named by him because in spite of its nitrogen content the compound resembled a hydrocarbon. It is isolated by distilling crude anthracene oil (282) with caustic potash by which it is converted into a potassium derivative.



The structure was confirmed by the production of carbazole by leading diphenylamine vapour through red hot tubes:



Dibenzopyrrole is obtained in almost quantitative yield by heating 2,2'-diaminodiphenyl with dilute sulphuric or hydrochloric acid to 200° (TAUBER). This reaction is analogous to the formation of diphenylamine from aniline (236).

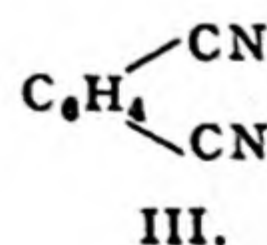
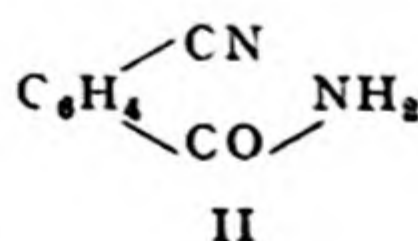
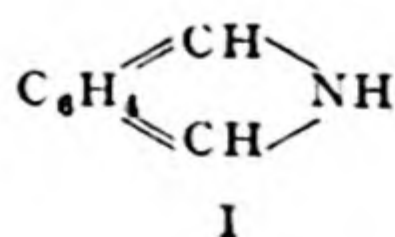
Carbazole melts at 238° , boils at 355° and sublimes easily; it forms a picrate which separates in large red crystals melting at 186° , but it shows no evidence of salt formation with hydrochloric acid. As a secondary amine it forms a nitroso-compound.

Carbazole dissolves in concentrated sulphuric acid with a yellow colour; if a trace of nitric or nitrous acid is present, the colour becomes an intense green. With concentrated sulphuric acid and isatin (315) a deep blue colour is produced.

Carbazole is of some importance for the preparation of dyestuffs, *e.g.* Hydron Blues.

Phthalocyanine dyes

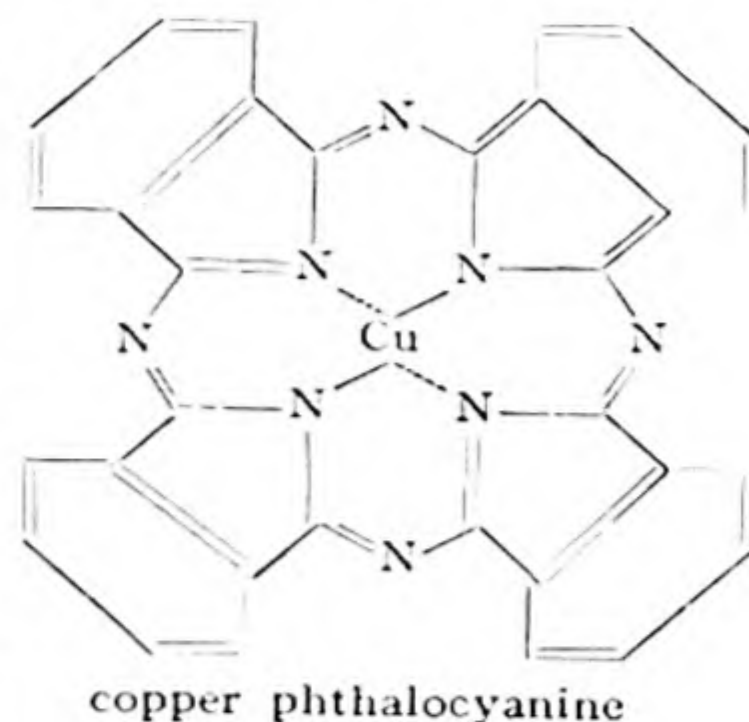
318. This important group of colouring matters may be considered as derivatives of iso-indole (I). They are formed by heating *o*-cyanobenzamide (II) or phthalonitrile (III) (LINSTED) with metals, *e.g.* Mg, Cu, etc., or their salts:



The most important is copper phthalocyanine (annexed formula). The structure of these compounds was suggested by LINSTED from chemical evidence and completely confirmed by ROBERTSON from a complete X-ray examination of single crystals.

The ring system in the phthalocyanines is very similar to that in the *porphyrins* (319). The phthalocyanines are therefore called *porphyrazines*, the copper compound being copper tetraphenylporphyrazine.

These insoluble, highly coloured compounds are used as pigments. Finely dispersed in water or oils they produce water or oil paints, printing inks, etc. They are also used for colouring articles directly, *e.g.* by incorporating the finely dispersed pigment into artificial leather, lacquers, soap, linoleum, etc. They are distinguished by their beautiful bright colours, their chemical stability and their fastness to light; in general properties they are akin to the best mineral pigments.



Haemin and the porphyrins

319. The colouring matter in the red blood corpuscles, *haemoglobin*, consists, as already mentioned in section 201, of an easily splittable compound of a protein, globin, and a colouring matter, *haem* or *haemochromogen*. Haem, $C_{34}H_{32}O_4N_4Fe$, has been obtained crystalline; the iron is divalent and combined as a complex. This colouring matter, which is also called *protohaem*, is a very unstable compound, which is oxidised by atmospheric oxygen extremely easily.

When *oxyhaemoglobin* or blood is treated with a saturated solution of common salt in acetic acid, a crystalline compound *haemin*, $C_{34}H_{32}O_4N_4FeCl$, is readily obtained. The iron atom is trivalent, two valency bonds being attached to nitrogen and the third ionogenically to the chlorine atom.

By the action of dilute alkalis on haemin, *haematin*, $C_{34}H_{32}O_4N_4FeOH$, is produced. This compound can also be produced by splitting oxyhaemoglobin with dilute acids. The salts of haematin are called *haemins*; the above mentioned chloride is sometimes called haemin for short.

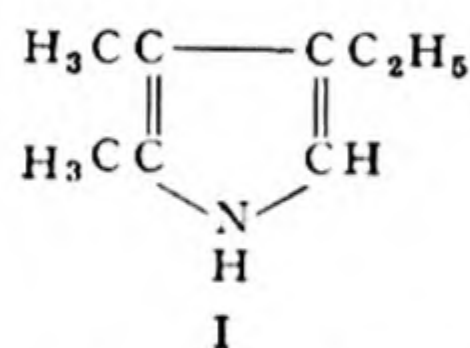
The chemistry of haemin has been studied by a large number of investigators and important contributions have been made, for example, by NENCKI, PILOTY, KÜSTER and WILLSTÄTTER. The structure of this and many closely related compounds was established by HANS FISCHER and

his pupils and eventually they were able to synthesise haemin (1929). Only a few of the main points can be mentioned here.

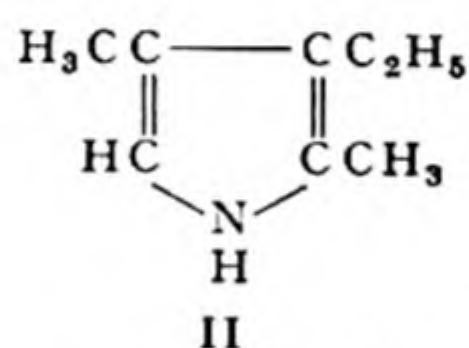
Structure of haemin. This compound is a dicarboxylic acid, both mono- and dimethyl esters being known. When haemin is treated with acids the coordinately combined iron is removed and a number of well-crystallised, coloured compounds, the *porphyrins*, are produced. These differ in composition according to the nature of the acid used for breaking down the haemin. Porphyrins are formed in the animal body under certain physiological and pathological conditions; various porphyrins occur also in the animal and vegetable kingdoms. They can be recognised by their characteristic absorption spectra.

By the further fission of haemin under reducing conditions, *e.g.* by the action of hydriodic acid and acetic acid or of tin and hydrochloric acid, the under-mentioned pyrrole derivatives, the structures of which have been established by synthesis, are produced.

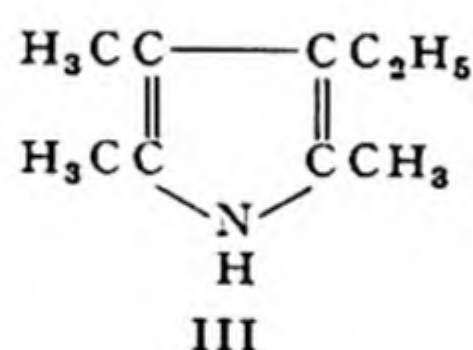
The yields in which these four pyrrole derivatives (I–IV) are obtained indicate that four pyrrole nuclei occur in haemin:



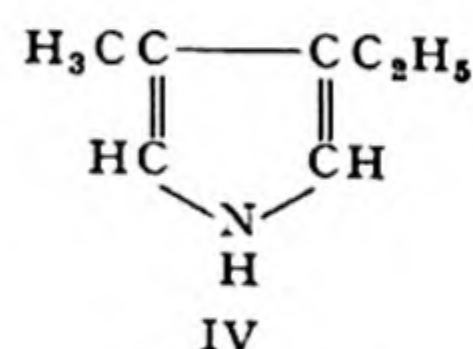
haemo-pyrrole



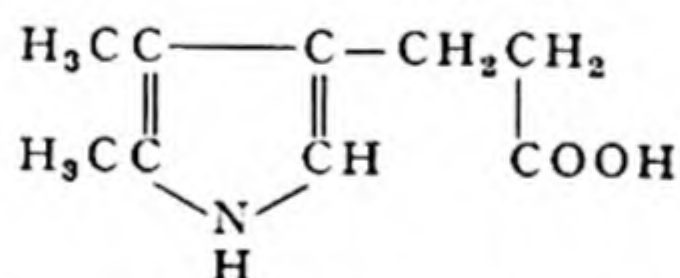
crypto-pyrrole



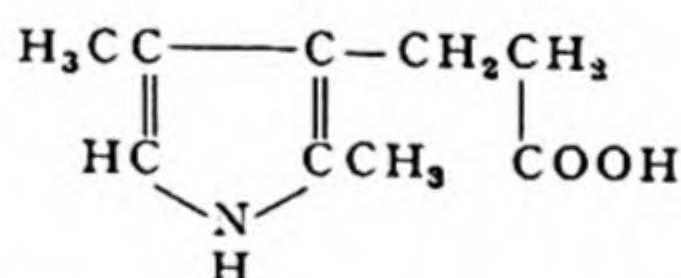
phyllo-pyrrole



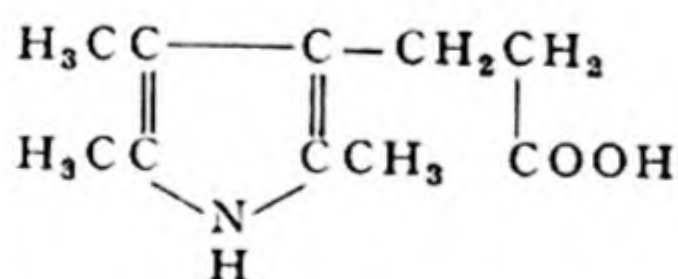
opso-pyrrole



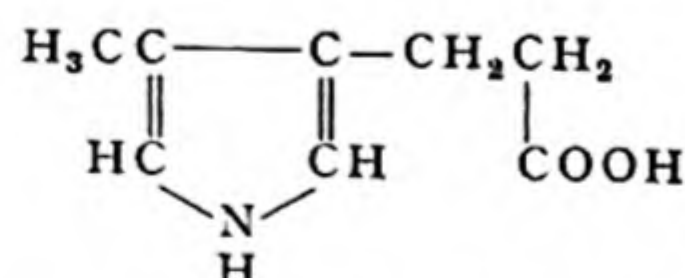
haemo-pyrrole carboxylic acid



crypto-pyrrole carboxylic acid



phyllo-pyrrole carboxylic acid

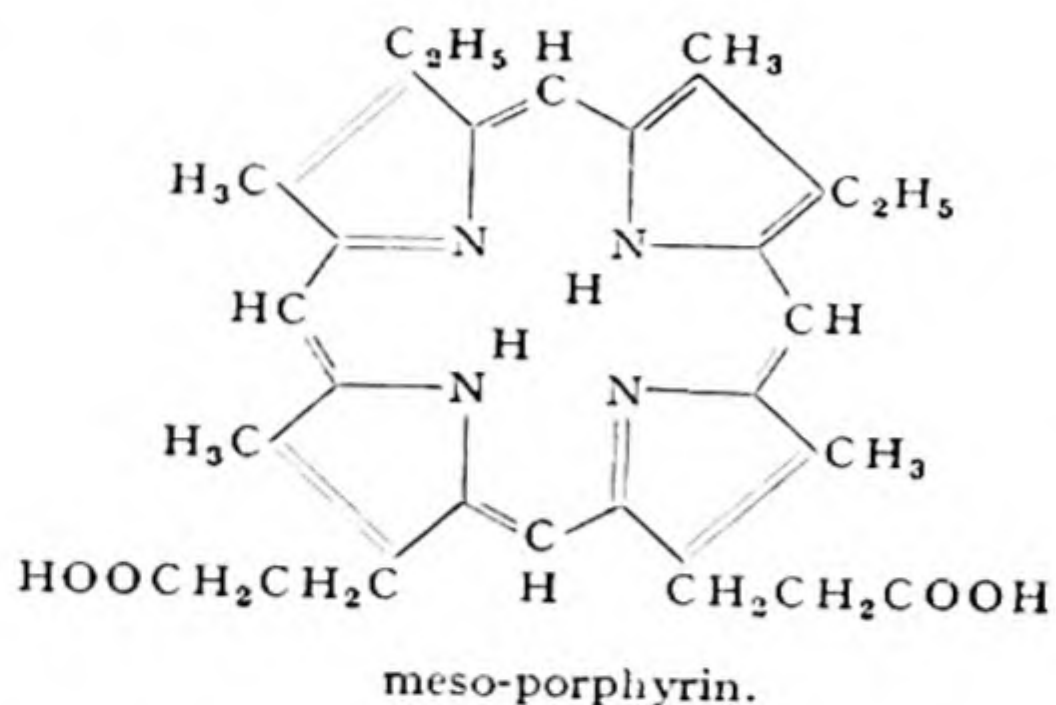
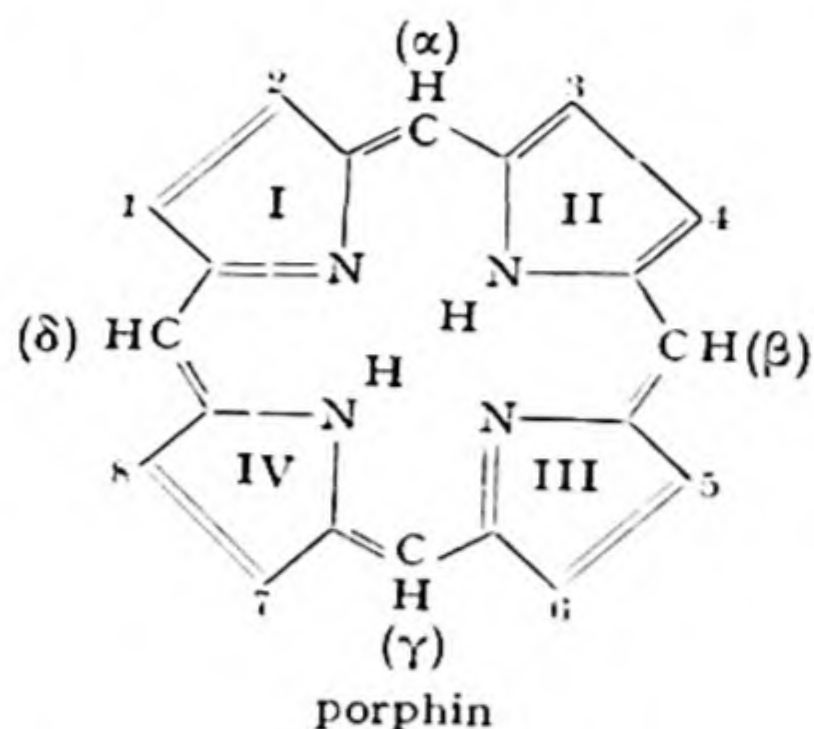


opso-pyrrole carboxylic acid.

By treating haemin carefully with a mixture of hydriodic acid, acetic acid and red phosphorus, *meso-porphyrin*, $\text{C}_{34}\text{H}_{38}\text{O}_4\text{N}_4$, is produced. When the compositions of these compounds are compared with one another it appears that the FeCl-group in haemin is replaced by two atoms of hydrogen and four additional atoms of hydrogen are taken up into the molecule. Two vinyl groups are present in haemin, which are converted into ethyl groups during the reductive fission. Like haemin, meso-porphyrin contains two

carboxyl groups, both of which can be esterified, so that the dimethyl ester of this compound is also known.

By decarboxylating meso-porphyrin, a compound of the composition $C_{32}H_{38}N_4$, m.p. $360-363^\circ$, *aetioporphyrin* III, is formed; the parent of this class of compounds is porphin, $C_{20}H_{14}N_4$:



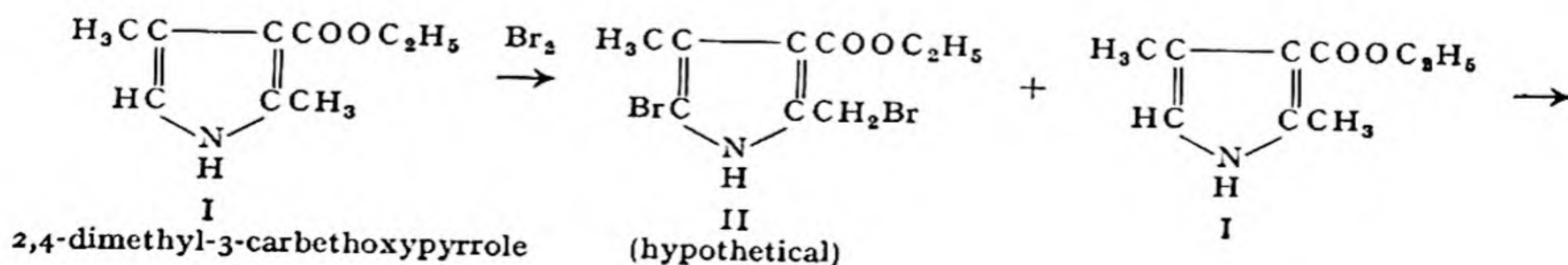
Structure of the porphyrins. The porphin ring system contains four pyrrole groups joined by methine groups. Porphin has been obtained in very small yield by H. FISCHER by heating an alcoholic solution of α - or 2-pyrrole-aldehyde with anhydrous formic acid. The carbon atoms of the aldehyde groups furnishes the CH-groups joining the pyrrole nuclei.

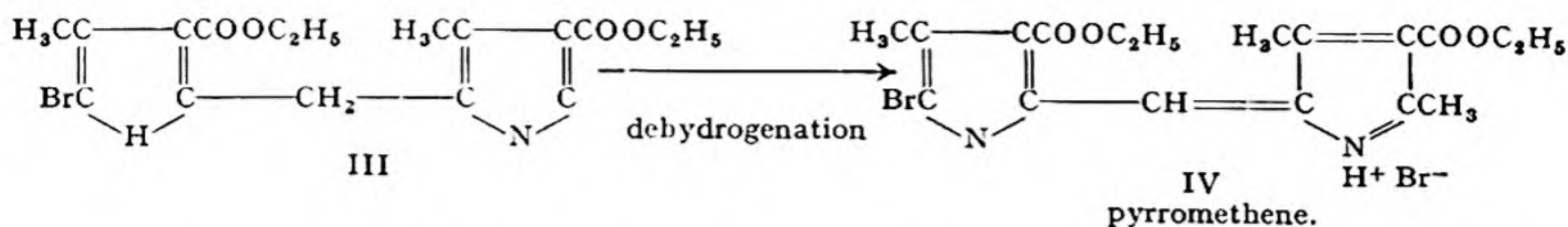
At the suggestion of H. FISCHER, the carbon atoms of the methine groups are differentiated by greek letters, the pyrrole nuclei by roman numbers and the substitutable carbon atoms in the pyrrole nuclei by arabic numbers (see formula above).

Before porphin was known, FISCHER had already made a large number of its substitution products, the porphyrins, synthetically.

The structure of the porphyrins is apparent by comparison with compounds of established structure by synthesis.

One of the synthetic methods followed, depends on the action of bromine on substituted pyrroles carrying a methyl group in position 2 or 5, while the other carbon atom (5 or 2) is unsubstituted. The substitution of bromine probably takes place on the carbon atom in the methyl group in position 2 or 5 and on the unsubstituted position 5 or 2, so that II is probably formed as an intermediate product:

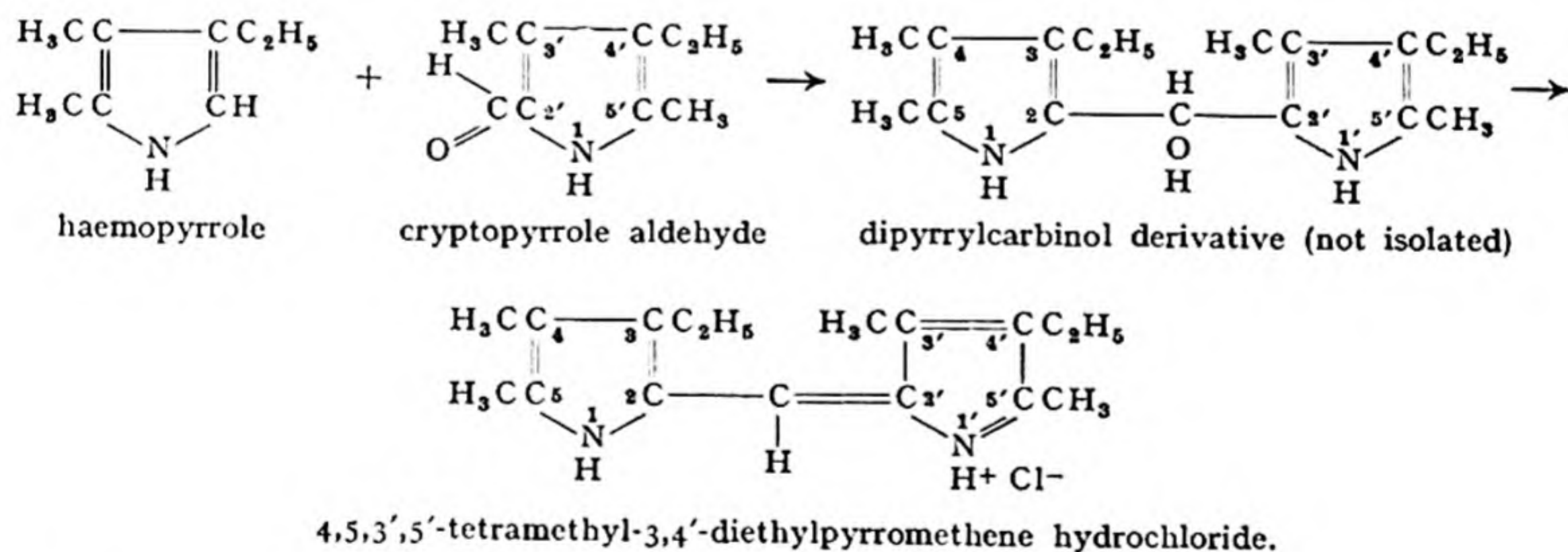




This hypothetical product reacts with a second molecule of I with the formation of a brominated *dipyrrylmethane* (III), which can also be obtained by other methods. Compounds of this type can be easily oxidised; in the process they are converted into *pyrromethenes*. The dipyrrromethane, which is assumed to be an intermediate product, is dehydrogenated by the excess bromine with the production of the hydrobromide of the brominated *pyrromethene* (IV). Hence this salt is obtained directly by the action of bromine on 2,4-dimethyl-3-carbethoxypyrrole (I).

The pyrromethenes are stable compounds giving well defined, crystalline salts.

320. Non-halogenated pyrromethenes are produced, for example, by condensing pyrrole aldehydes with pyrroles containing no substituents in the 2 or 5 position (*i.e.* containing a CH-group). Thus the hydrochloride of 4,5,3',5'-tetramethyl-3,4'-diethylpyrromethene is produced from cryptopyrrole aldehyde and haemopyrrole in alcoholic hydrochloric acid:

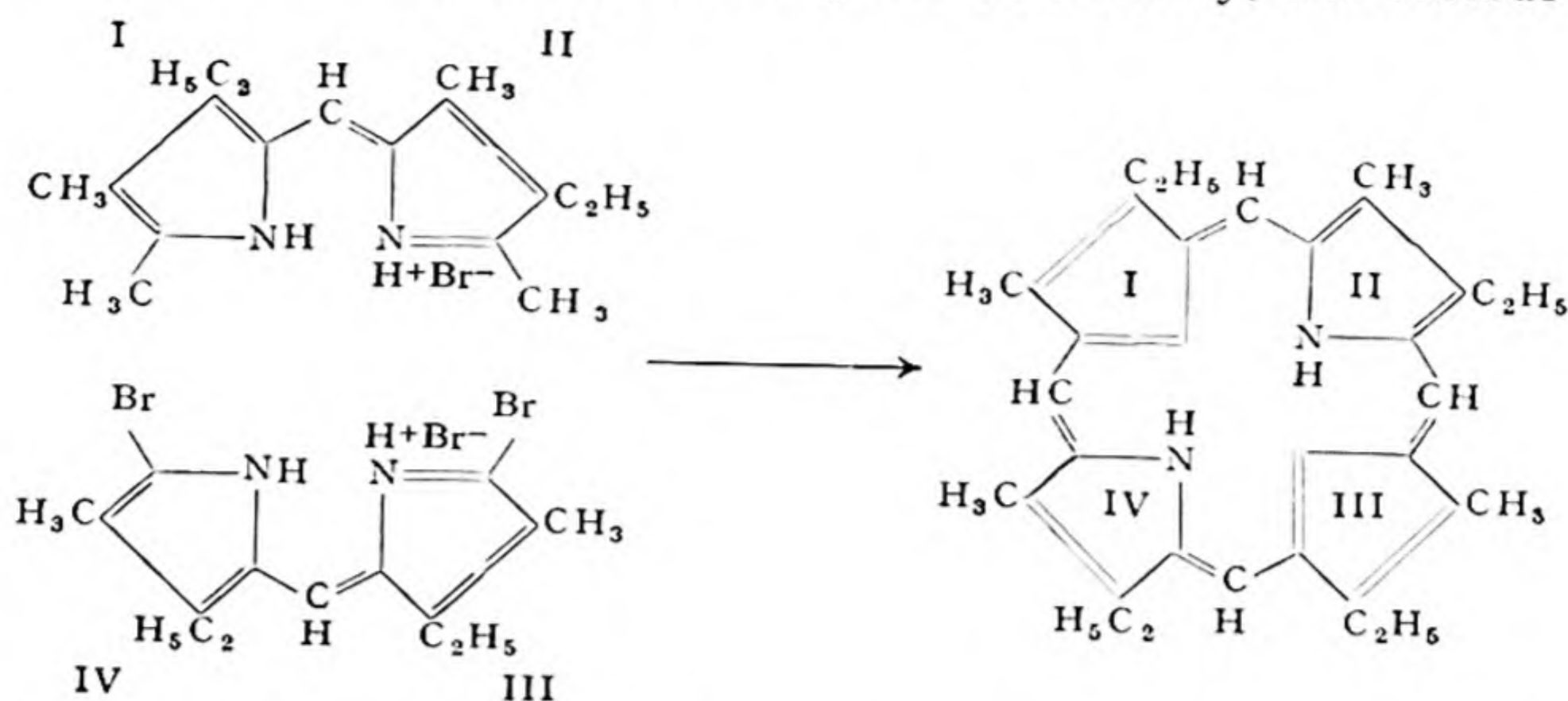


When the hydrobromide of this pyrromethene is heated to 140° with glacial acetic acid, hydrogen bromide and an equivalent quantity of 5,5'-dibromo-4,4'-dimethyl-3,3'-diethylpyrromethene hydrobromide, *aetioporphyrin* III, is produced.

In this reaction apparently, dehydrogenation also takes place as well as ring closure with the elimination of hydrogen bromide.

The pyrrole nuclei I and II in aetioporphyrin have their origin in the 4,5,3',5'-tetramethyl-3,4'-diethylpyrromethene hydrobromide, and the pyr-

role nuclei III and IV in the 5,5'-dibromo-4,4'-dimethyl-3,3'-diethylpyrromethene hydrobromide. In order to express this clearly, the various nuclei



of these compounds are marked with roman ordinals in the reaction scheme given above.

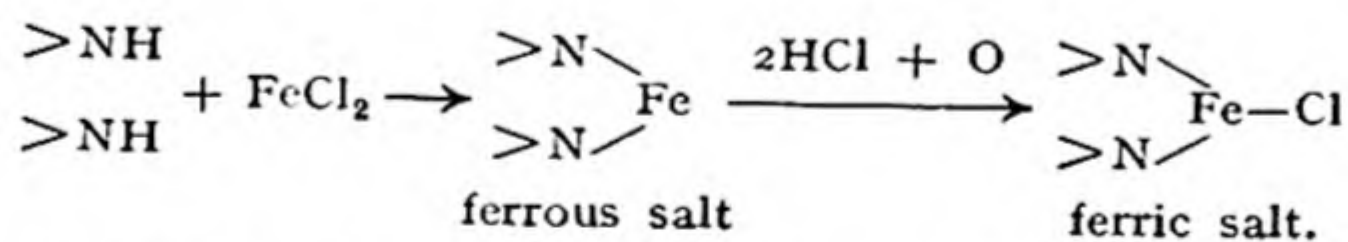
The numbering of the carbon atoms in pyrromethenes is not in accordance with the general rule (clockwise numbering), both the pyrrole nuclei in the pyrromethenes are numbered in the opposite direction by FISCHER.

This aetioporphyrin or 1,3,5,8-tetramethyl-2,4,6,7-tetraethylporphin is identical, as regards crystallographic properties and absorption spectrum, with the product prepared from haemin.

A large number of porphyrins have been prepared by various methods; in many cases the structure has been established by two independent syntheses.

Iron combined as a complex can be introduced into the porphyrins by heating them in solution in glacial acetic acid with ferrous acetate and common salt.

The product formed initially, is a complex ferrous salt, which is very easily oxidised and is converted into the chloride, so that a complex ferric salt crystallises out as represented below:

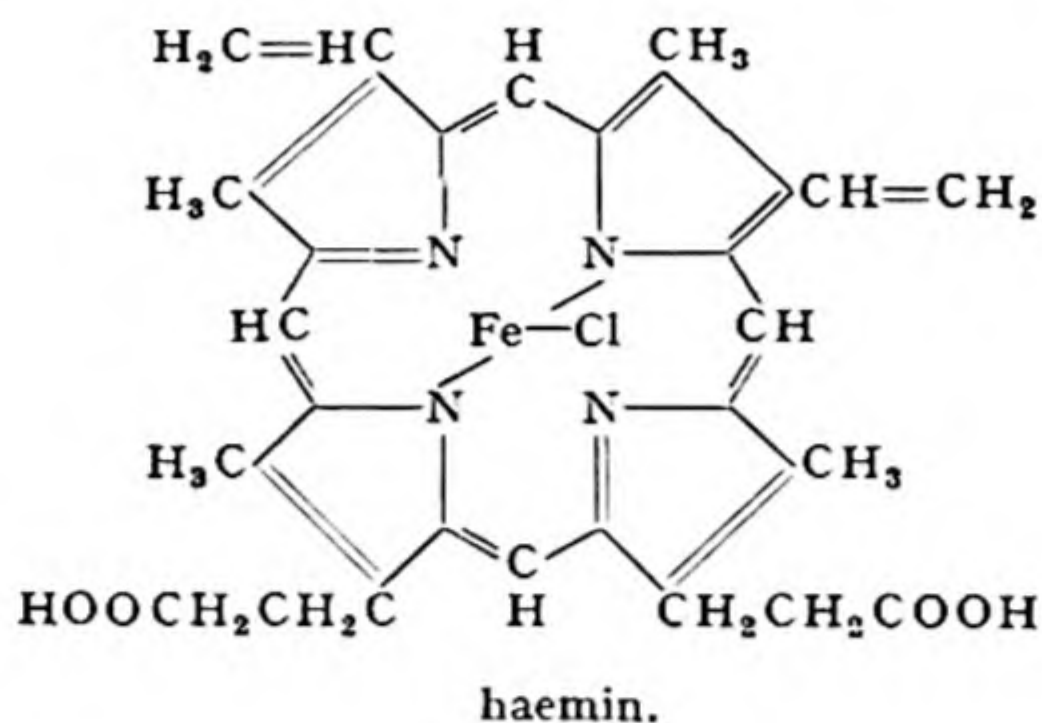


Other complex metallic salts, *e.g.* Cu, Mg, Zn, Cd, Sn, Ag, Co, V, of porphyrins are known. These complex salts as a rule crystallise very well; they may be distinguished from the porphyrins by their absorption spectra.

On the next page is given the proved structure of haemin. Only this structure is given since a discussion of the synthesis would take us too far at this stage.

From this formula it is easily to be seen that both the pyrroles and their carboxylic acids from which the structure is given in 314, can originate from haemin by reductive fission.

In the molecules of haemin, porphin and the porphyrins there is a heterocyclic ring of sixteen atoms, formed from twelve carbon atoms and four nitrogen atoms. These molecules contain an uninterrupted system of conjugated



double bonds, which is responsible for the intense colour of these substances. Of the naturally occurring porphyrins the following may be mentioned:

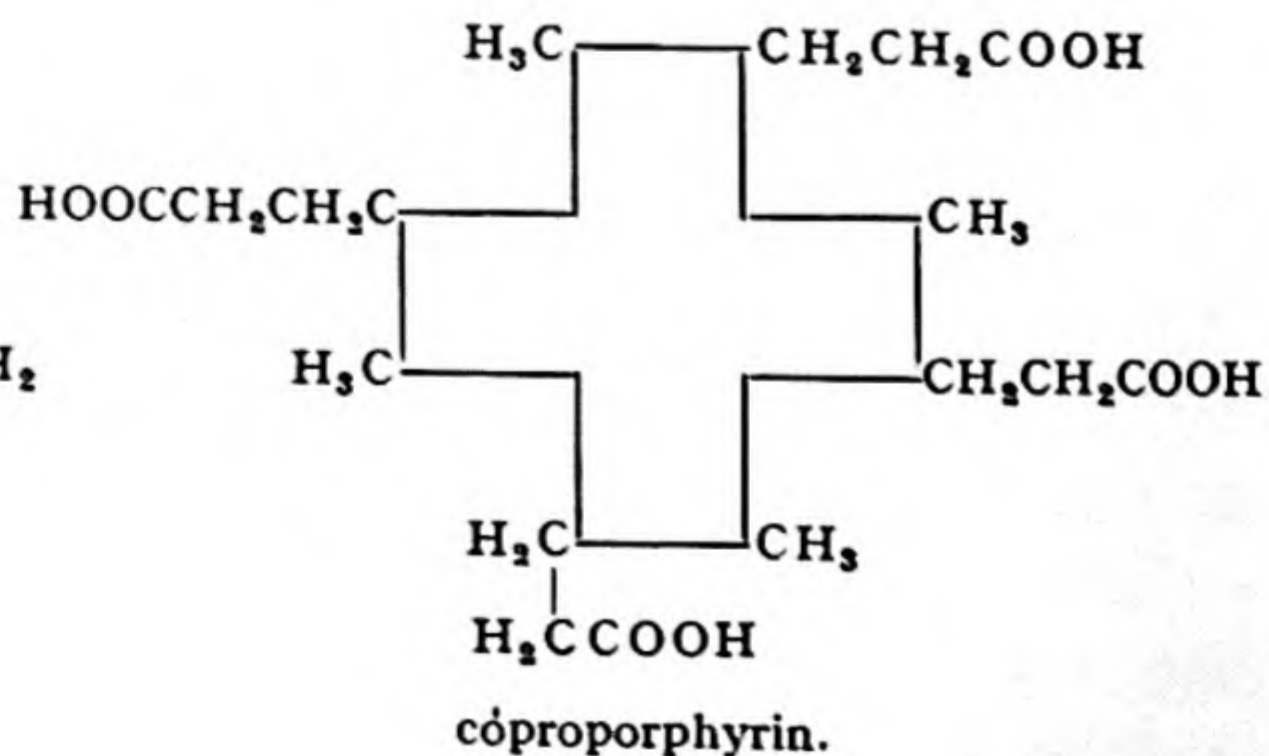
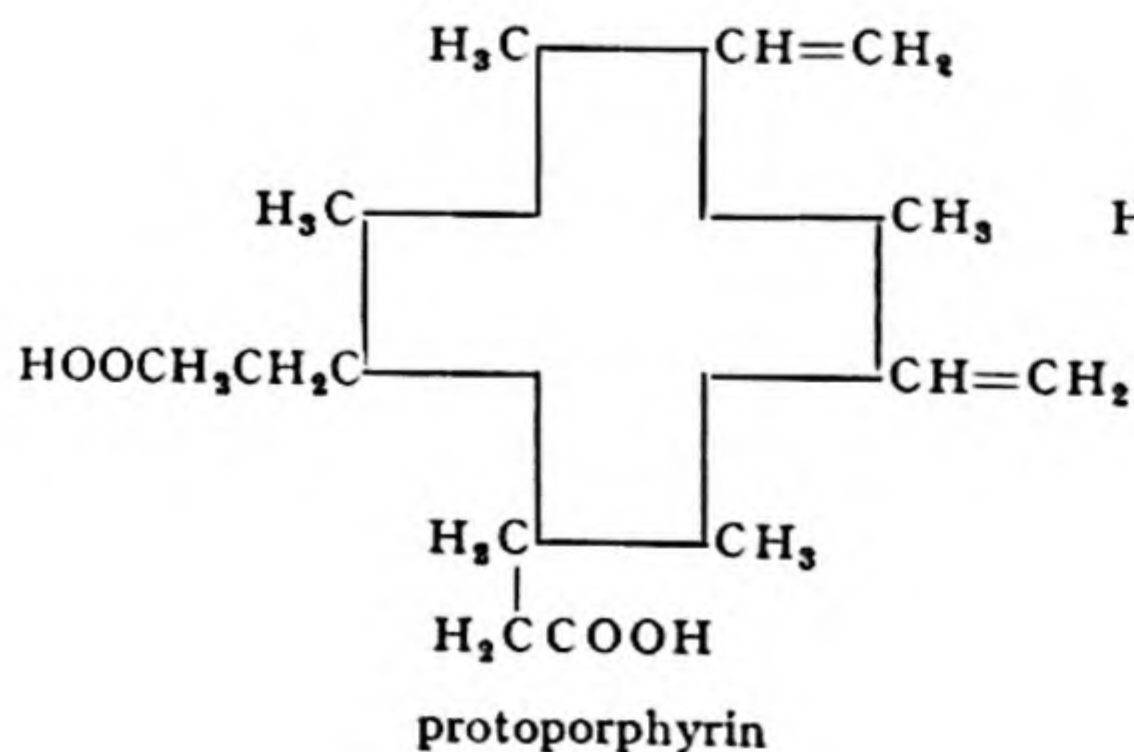
Protoporphyrin $C_{34}H_{34}O_4N_4$, a dicarboxylic acid, crystallises in brownish yellow crystals. It occurs in the vegetable kingdom, *e.g.* in peas, maize, oats and also in yeast. The shells of various birds' eggs also contain protoporphyrin and it occurs in very small amounts in human faeces. It can be produced by careful decomposition of haemin and has been prepared by synthesis.

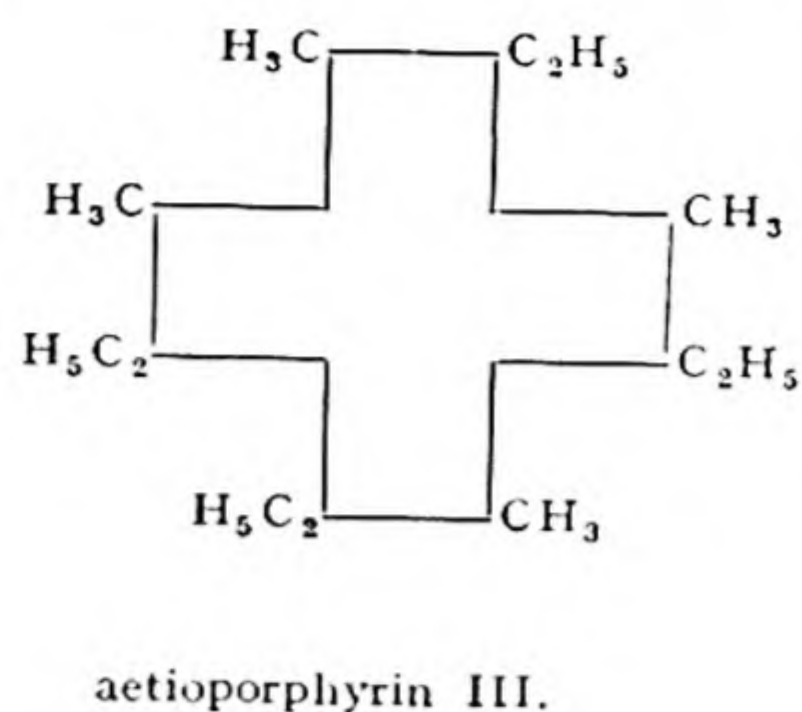
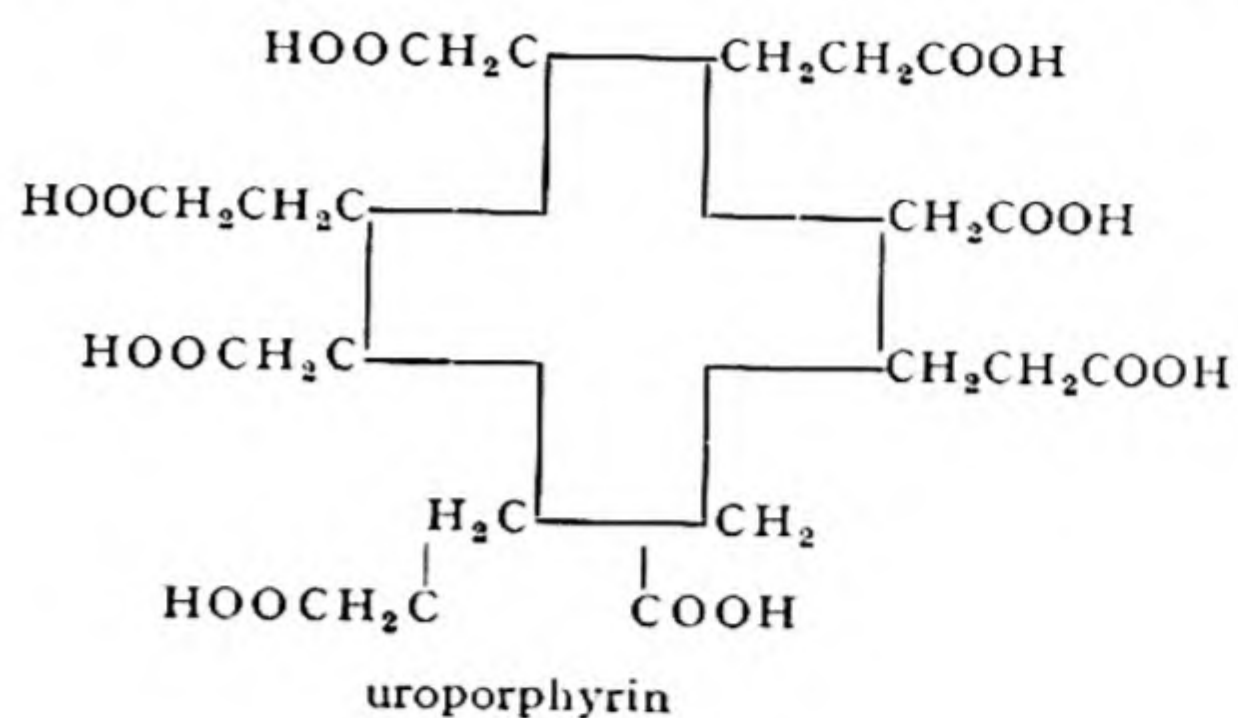
Coproporphyrin $C_{36}H_{38}O_8N_4$, a tetra-carboxylic acid occurs in yeast and human faeces; it occurs also in urine in certain pathological conditions.

Uroporphyrin $C_{40}H_{38}O_{16}N_4$, an octa-carboxylic acid, also occurs in urine in certain pathological conditions. A complex copper derivative of uroporphyrin occurs in the feathers of certain birds.

Complex vanadium salts of porphyrins and also aetioporphyrin occur in very small quantities in some kinds of coal and petroleum.

The structural formulae of the porphyrins can be represented in an abbreviated form by a device of H. FISCHER. A pyrrole nucleus is represented by the sign \square and the methine groups are not drawn in:





Colouring matters of leaves

The Chlorophylls

321. Two green and two yellow pigments occur in the chloroplasts. The yellows are carotene and xanthophyll (308); the green colouring matters are the bluish green *chlorophyll-a* $\text{C}_{55}\text{H}_{72}\text{O}_5\text{N}_4\text{Mg}$, and the yellowish green *chlorophyll-b* $\text{C}_{55}\text{H}_{70}\text{O}_6\text{N}_4\text{Mg}$.

These substances were first isolated from green leaves by R. WILLSTÄTTER. By his investigations (1904-1917) followed by those of CONANT and especially by those of H. FISCHER, the structures of the chlorophylls can now be taken as virtually established.

The four colouring matters mentioned above occur in all green plants from the single celled green algae to the very complex phanerogamia.

The ratio of chlorophyll-*a* : -*b* is about 3 : 1, the ratio of chlorophyll (*a* + *b*) : (xanthophyll + carotene) is also about 3 : 1. Carotenoids predominate, however, in autumn leaves.

Properties and structure of the chlorophylls. Both are very easily decomposed by the action of dilute acids; the complexly bound magnesium is split off as magnesium oxide and replaced by two atoms of hydrogen.

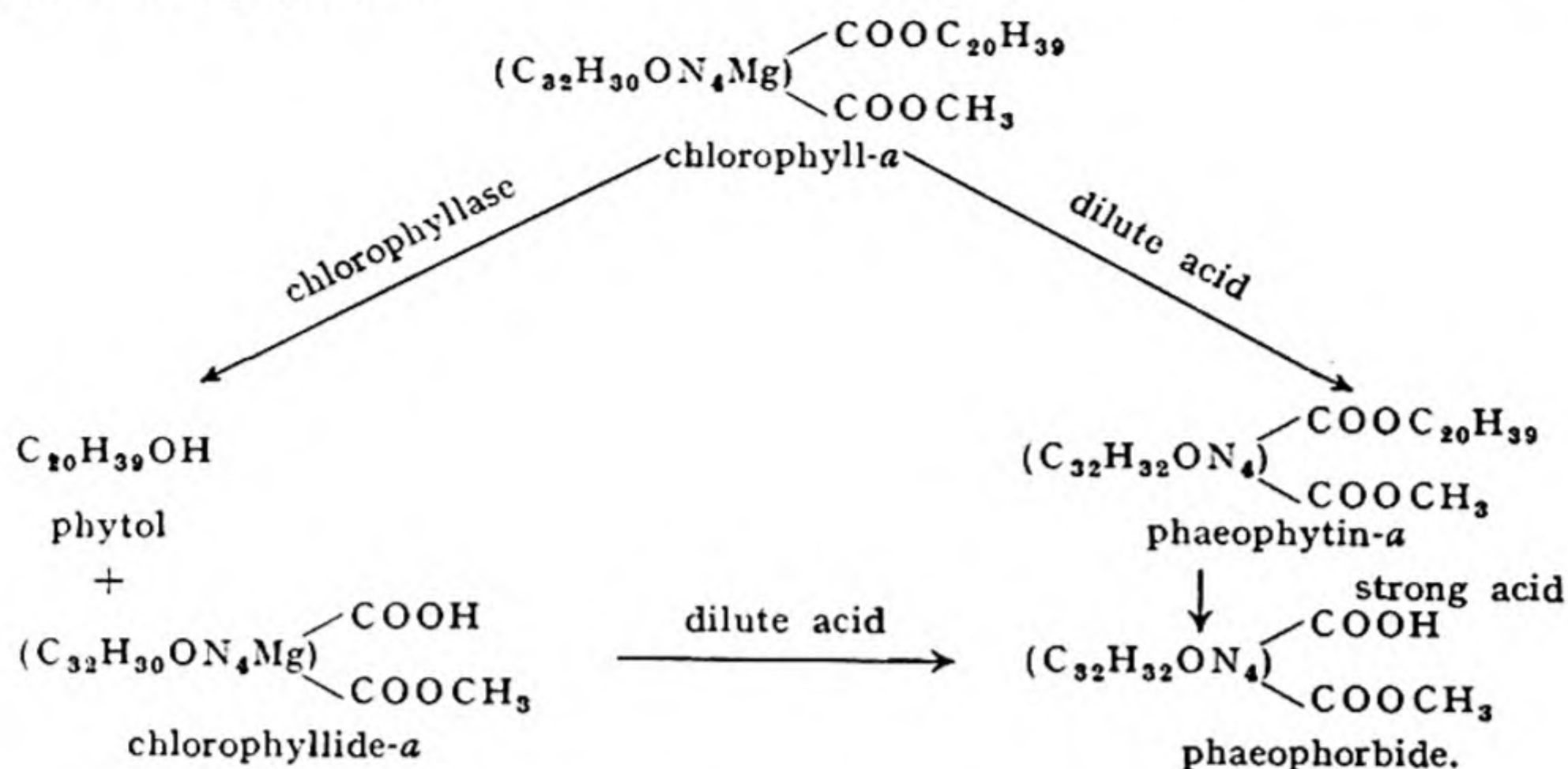
Phaeophytin-a $\text{C}_{55}\text{H}_{74}\text{O}_5\text{N}_4$, is produced from chlorophyll-*a*, into which it is reconverted by treatment with an alkylmagnesium halide.

Phaeophytin-b $\text{C}_{55}\text{H}_{72}\text{O}_6\text{N}_4$, is produced from chlorophyll-*b*.

In the following paragraphs the discussion will be limited to a few reactions of chlorophyll-*a*, which are of importance for determining the structure of this substance. The determination of the structure of chlorophyll-*b* depends in the main on a similar series of reactions.

Chlorophyll-*a* is split up by an enzyme occurring in green plants, into phytol (95) and a compound, *chlorophyllide-a*, with one free carboxyl group and a carbomethoxyl group. Conversely, chlorophyll-*a* can be obtained from

phytol and chlorophyllide-*a* under the influence of the enzyme in question, namely, *chlorophyllase*:

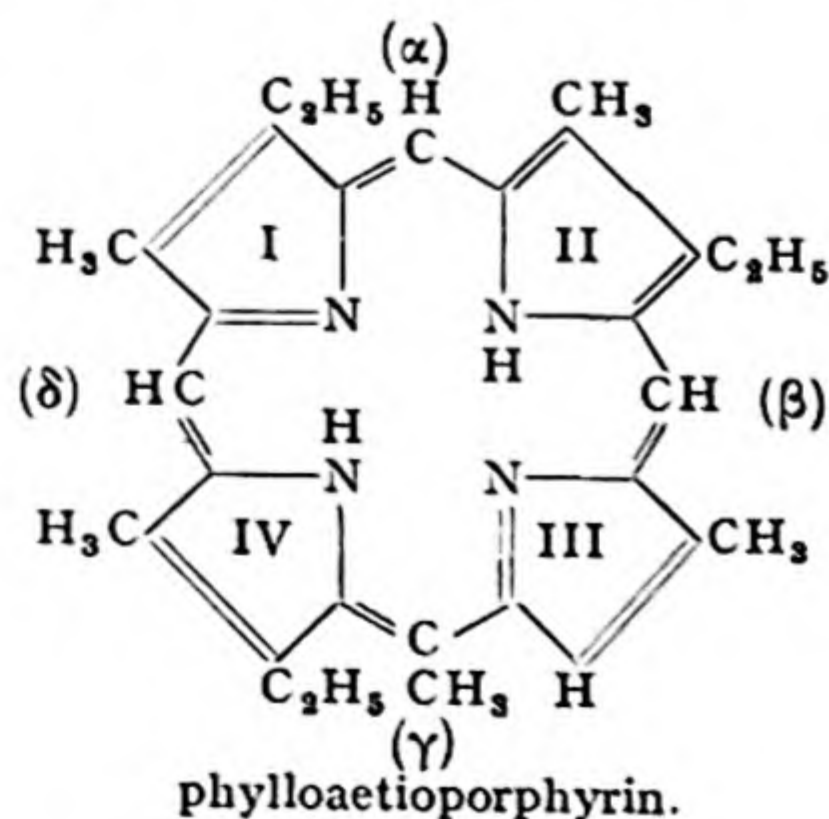
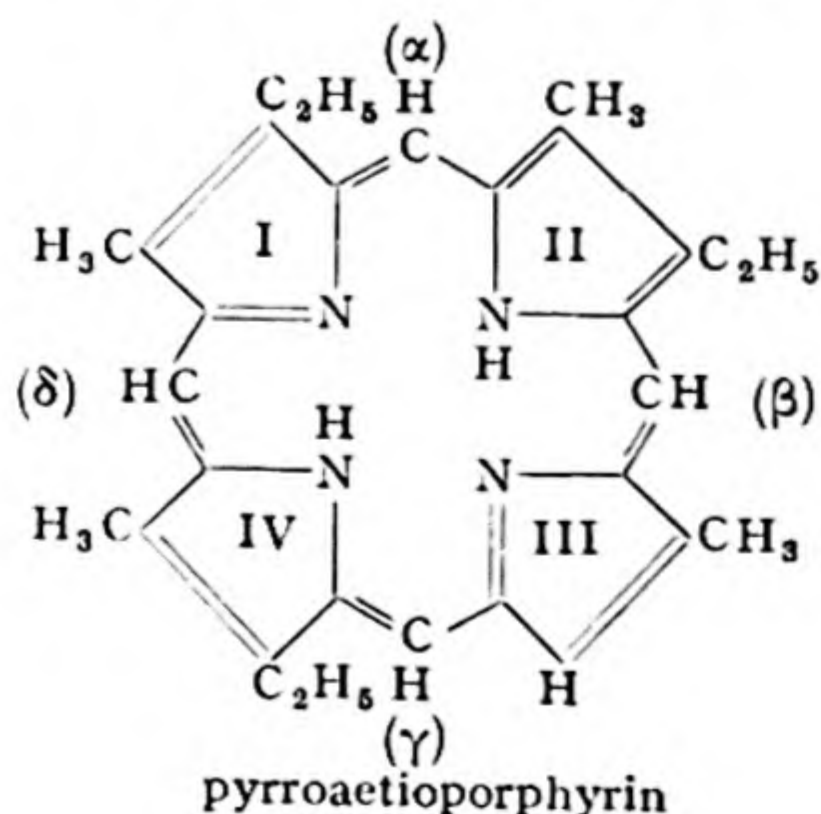


From this reaction scheme it is seen that chlorophyll is the ester of a dicarboxylic acid.

The COOCH_3 -group in chlorophyllide can be hydrolysed by alkalis but an alteration in the molecule then takes place. The phytol residue can be split off from phaeophytin by acid hydrolysis with the formation of *phaeophorbide*, which is also produced by removing the magnesium from chlorophyllide by the action of dilute acids.

A group of atoms consisting of 32 carbon atoms and 4 nitrogen atoms occurs in all the above formulae. On reductive fission, chlorophyll derivatives furnish the same pyrrole homologues as haemin (319). Hence this makes it probable that each of the four nitrogen atoms in chlorophyll is associated with a pyrrole nucleus.

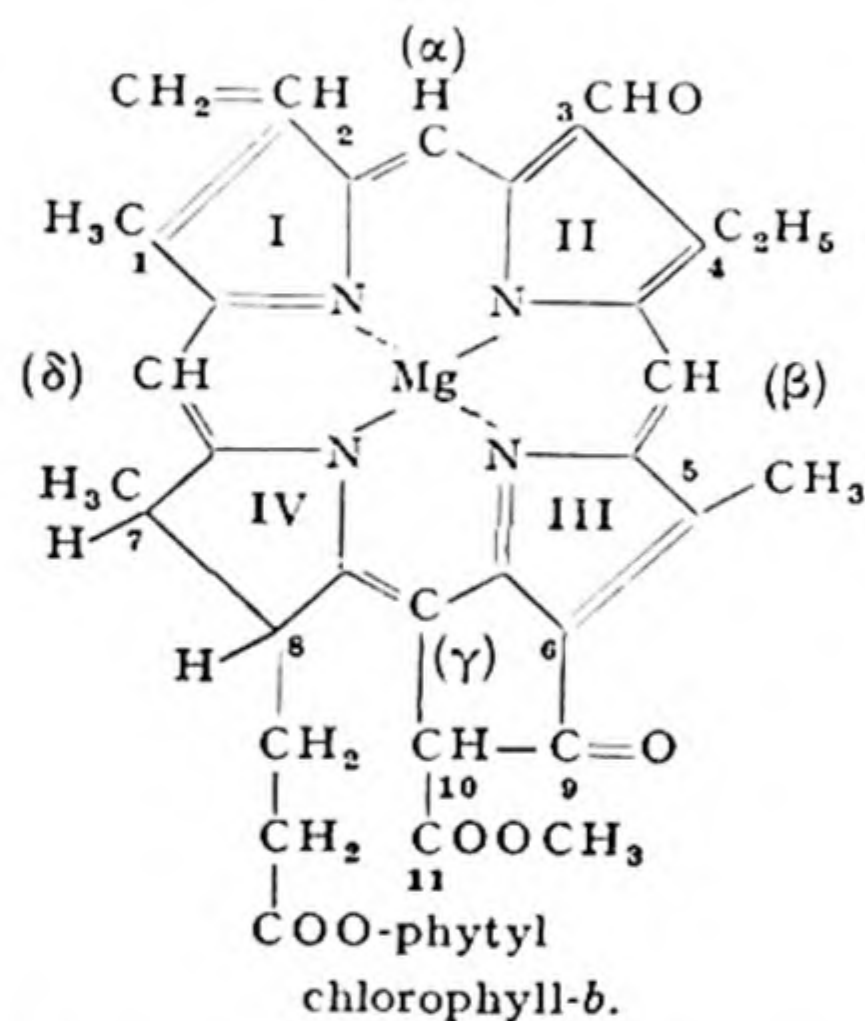
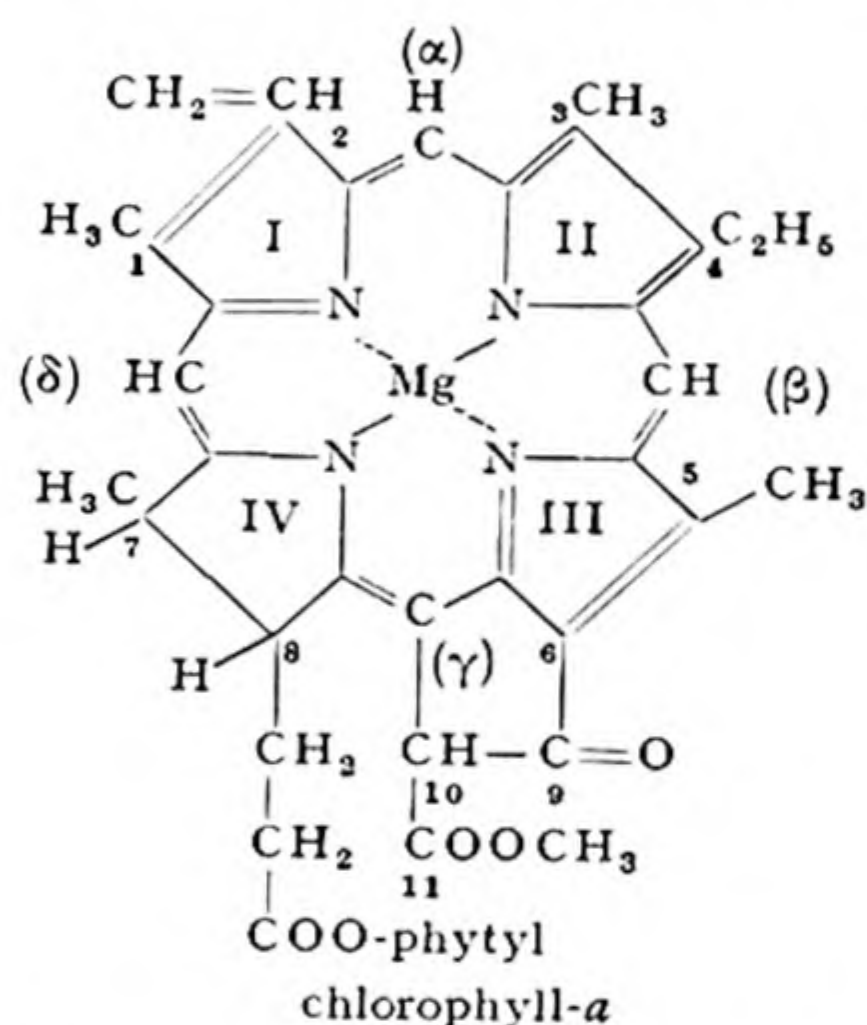
On further degradation of phaeophorbide with alkalis, various porphyrins (319) are produced with one or two carboxyl groups in the side chains; by removing carbon dioxide, two aetioporphyrins are eventually obtained, *pyrroaetioporphyrin* $\text{C}_{30}\text{H}_{34}\text{N}_4$, and *phylloaetioporphyrin* $\text{C}_{31}\text{H}_{36}\text{N}_4$:



From this, the great similarity in structure of chlorophyll and haemin, as regards the heterocyclic ring-system in both compounds, is at once evident.

In chlorophyll, another five carbon atom ring occurs condensed with the pyrrole nucleus III. A consideration of the derivation of the structure of chlorophyll is too involved for this book, and below is given simply the structural formulae, which agree best with the reactions of chlorophyll at present known.

Both chlorophyll-*a* and chlorophyll-*b* contain a dihydroporphyrin ring, in which carbon atoms 7 and 8 each carry a hydrogen atom. Chlorophyll-*a* has a methyl group on carbon atom 3, while chlorophyll-*b* carries an aldehyde or formyl group on this carbon atom. Otherwise, chlorophyll-*a* and chlorophyll-*b* are similar in structure:



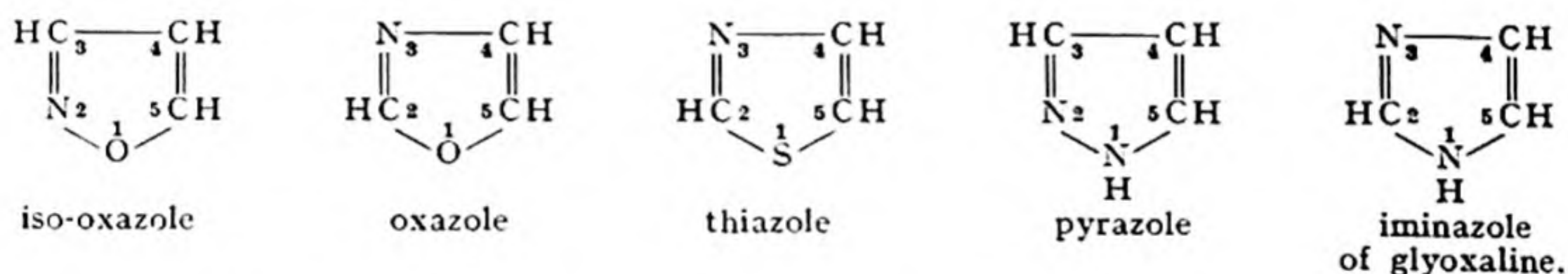
The phytyl residue present in chlorophyll is the cause of the solubility of the latter in oils and its resemblance to the carotenes (308).

CHAPTER 12

FIVE-RING SYSTEMS WITH TWO HETERO-ATOMS IN THE RING

322. To this group belong, for example, compounds containing rings in which an oxygen and a nitrogen atom, or a sulphur atom and a nitrogen atom, or two similar atoms, such as two nitrogen atoms, occur.

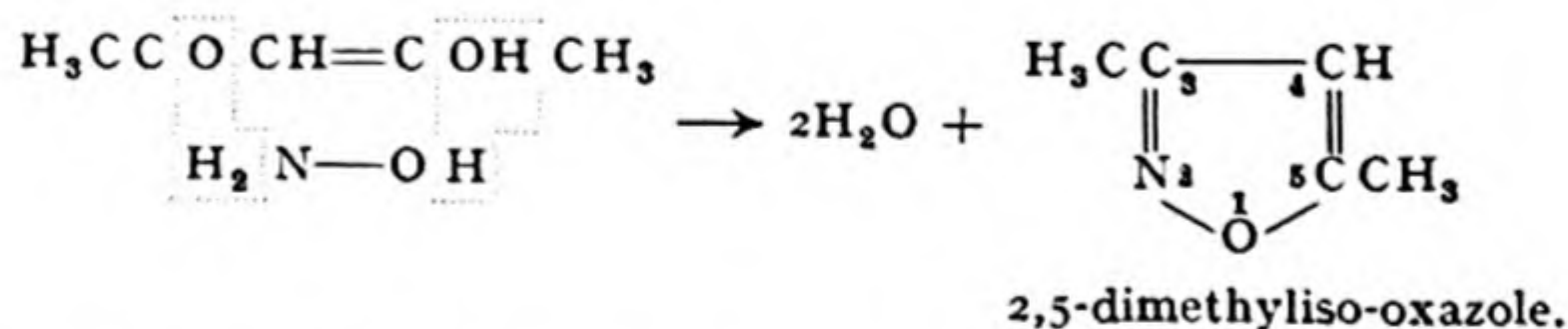
To a greater or lesser degree, compounds containing these ring-systems are similar in properties to aromatic compounds. The following types will be discussed briefly:



(i) ISO-OXAZOLE, OXAZOLE AND THEIR DERIVATIVES

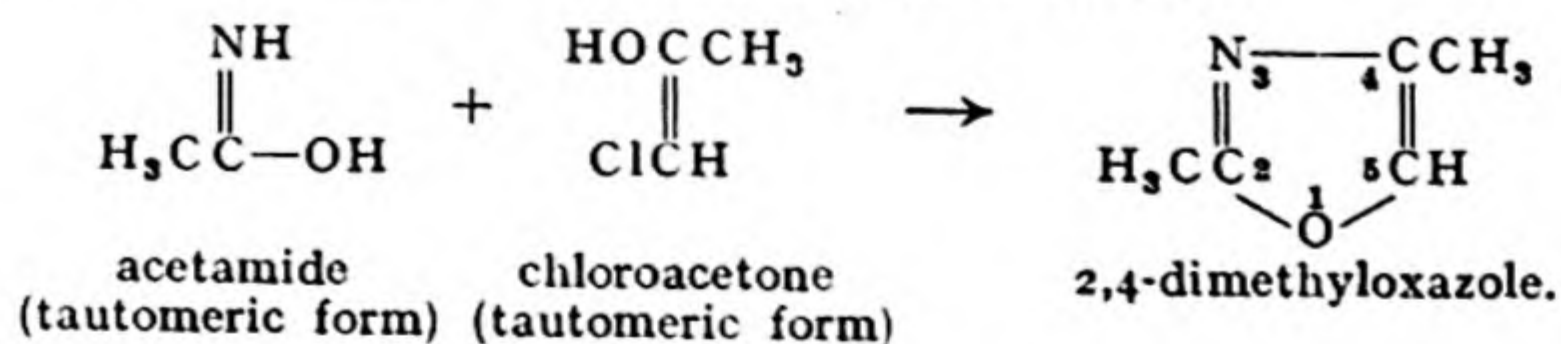
Iso-oxazole C_3H_3ON and its alkyl derivatives are liquids, which are partly miscible with water and smell rather like pyridine.

Derivatives of iso-oxazole are obtained by the interaction of hydroxylamine on 1,3-diketones (**146**):



A compound with a condensed iso-oxazole ring is mentioned in **259**.

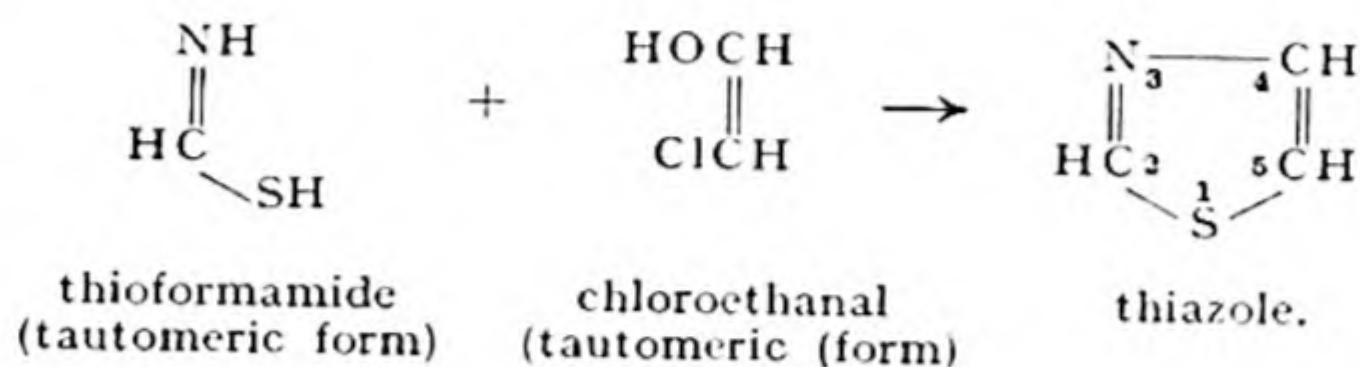
Oxazole C_3H_3ON , is unknown; its derivatives can be obtained, however, in various ways, *e.g.* by condensing amides with 1-halogenoketones:



2,4-Dimethyloxazole is a colourless liquid boiling at 108° , which is readily soluble in water, alcohol, and ether.

(ii) THIAZOLE AND ITS DERIVATIVES

Thiazole C_3H_3NS , like its derivatives, is a stable compound, which shows a great similarity in physical and chemical properties to pyridine (332). It boils at 117° and is miscible with water and the usual organic solvents. Thiazole and its derivatives can be prepared by the HANTZSCH synthesis by condensing thioamides with 1-halogenoaldehydes or ketones. Thiazole is obtained from thioformamide and chloroethanal:



Thiazole is not attacked by concentrated nitric acid. The alkylthiazoles are oxidised by potassium permanganate, the ring system being ruptured with the formation of sulphuric acid.

2-Bromothiazole is produced by the action of bromine on thiazole at 400° . This reaction is similar to the bromination of pyridine (335).

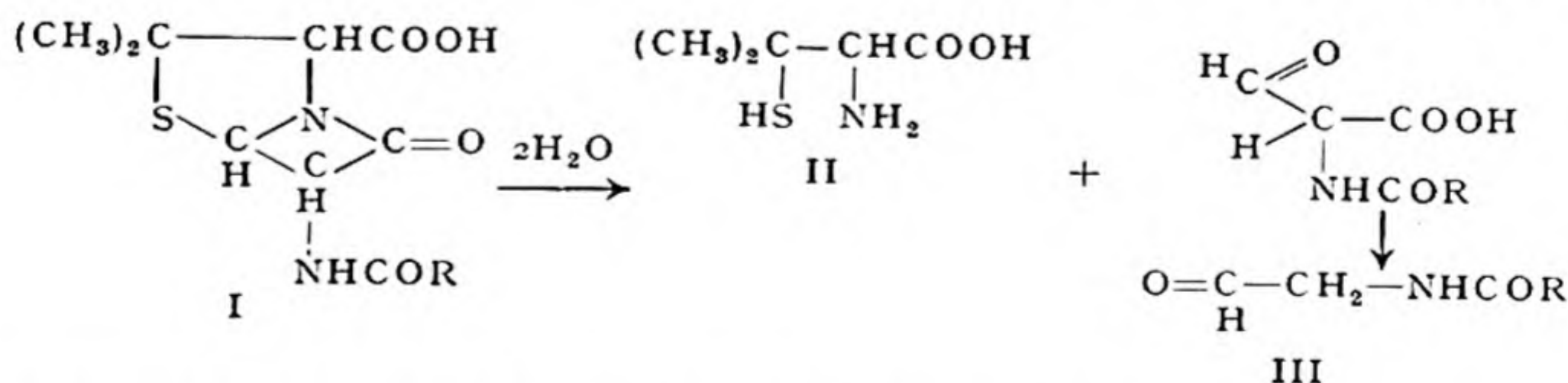
The thiazole ring occurs in aneurin, vitamin- B_1 (345).

Penicillin $C_9H_{11}O_4N_2SR$ belongs to a group of important antibiotics (see 241, 254, 335). The structure of this compound has been elucidated but the substance has not yet been synthesised. This substance is excreted by moulds. It was discovered in 1929 by FLEMING but was not then isolated. It was during the second world war that chemists in England and in America succeeded, as a result of an all out effort, in producing this substance in large quantities for combatting infectious diseases.

Besides a thiazolidine ring the molecule of penicillin contains a side-chain (R); this side-chain differs in penicillins from different sources (see Table 51). The formula I is now given to penicillin.

Each of the penicillins gives by hydrolytic fission penicillamine and a penilloaldehyde (III).

Penicillamine $C_5H_{11}O_2NS$, was the first degradation product of penicillin to be obtained in a crystalline state. Its structure (II) has been confirmed by synthesis:



The *penilloaldehyde* $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CONHCH}_2\text{CHO}$ was isolated in England from Δ^2 -*pentenylpenicillin*. The penilloaldehyde $\text{C}_6\text{H}_5\text{CH}_2\text{CONHCH}_2\text{CHO}$ is derived from American penicillins.

The penicillins are strong monobasic acids with $p_H \sim 2.9$. They are resistant towards reducing agents but are quickly broken down by oxidising agents.

TABLE 51

OBSERVED SIDE-CHAINS IN PENICILLINS

Penicillin	Formula of side-chain	Empirical formula
Δ^2 -Pentenylpenicillin	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2-$	$\text{C}_{14}\text{H}_{20}\text{O}_4\text{N}_2\text{S}$
Δ^3 - " "	$\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_2-$	$\text{C}_{14}\text{H}_{20}\text{O}_4\text{N}_2\text{S}$
<i>n</i> -Pentyl " "	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	$\text{C}_{14}\text{H}_{22}\text{O}_4\text{N}_2\text{S}$
<i>n</i> -Heptyl " "	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	$\text{C}_{16}\text{H}_{26}\text{O}_4\text{N}_2\text{S}$
Benzyl " "	$\text{C}_6\text{H}_5\text{CH}_2-$	$\text{C}_{16}\text{H}_{18}\text{O}_4\text{N}_2\text{S}$
<i>p</i> -Hydroxybenzyl penicillin	$\text{HOC}_6\text{H}_4\text{CH}_2-$	$\text{C}_{16}\text{H}_{18}\text{O}_5\text{N}_2\text{S}$

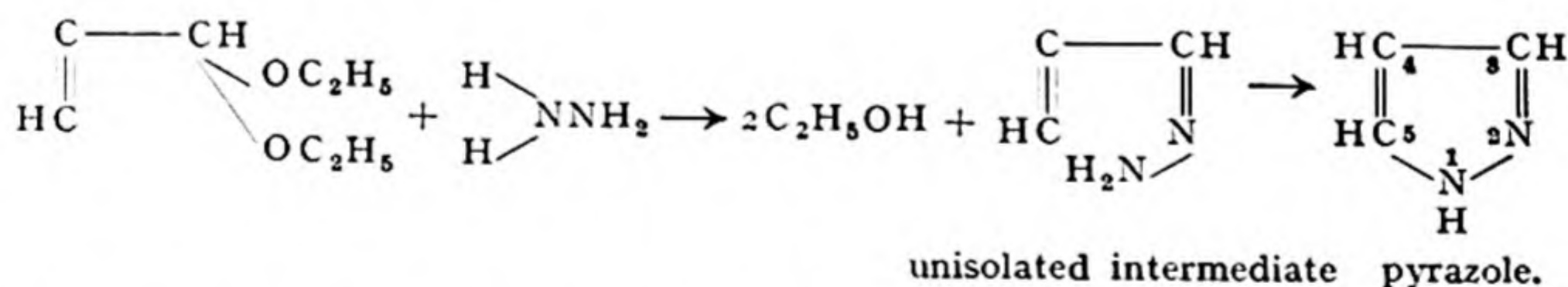
(iii) PYRAZOLE AND ITS DERIVATIVES

333. Many compounds are known in which the pyrazole ring system occurs. In synthesising these substances the ring nitrogen atoms are usually furnished by hydrazine or one of its derivatives. KNORR obtained the first derivative of pyrazole in 1883 starting from phenylhydrazine (247).

The name pyrazole, which was suggested by KNORR, indicates that this compound may be regarded as having been derived from pyrrole by replacing one of the nuclear methine groups by an atom of nitrogen.

Pyrazole $\text{C}_3\text{H}_4\text{N}_2$, melts at 70° and boils at 185° . It has an odour similar to that of pyridine and is readily soluble in water, alcohol, ether and benzene.

Method of preparation and structure. Pyrazole is produced by the action of hydrazine on 1,1-diethoxypropyne, the course of the reaction being represented as follows:



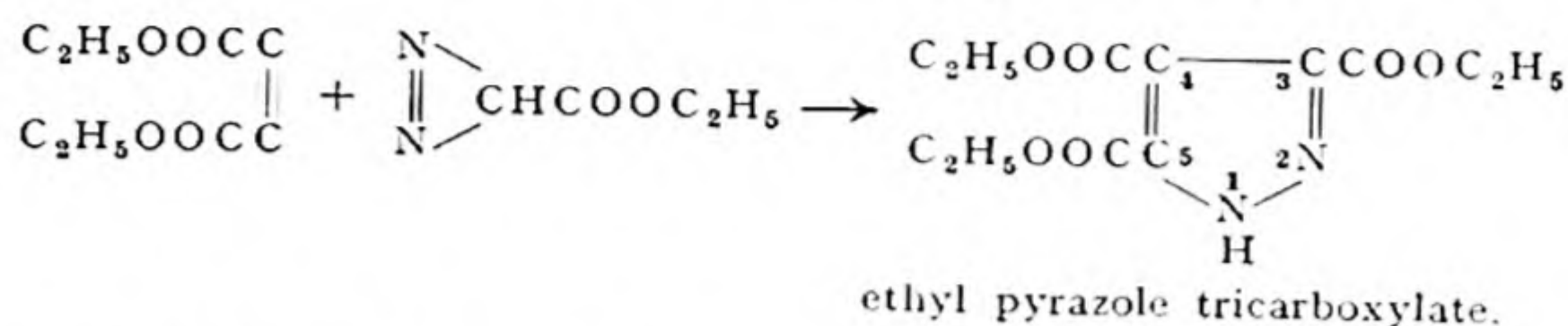
The structure follows from this method of preparation.

Properties of pyrazole. This compound is a very weak mono-acidic base, which shows a neutral reaction in aqueous solution. Pyrazole resembles aromatic compounds more than pyrrole. It is stable towards alkaline permanganate and can be sulphonated by fuming sulphuric acid and nitrated with nitric acid. The halogen atom in the monohalogeno-compounds can be made to react only with great difficulty.

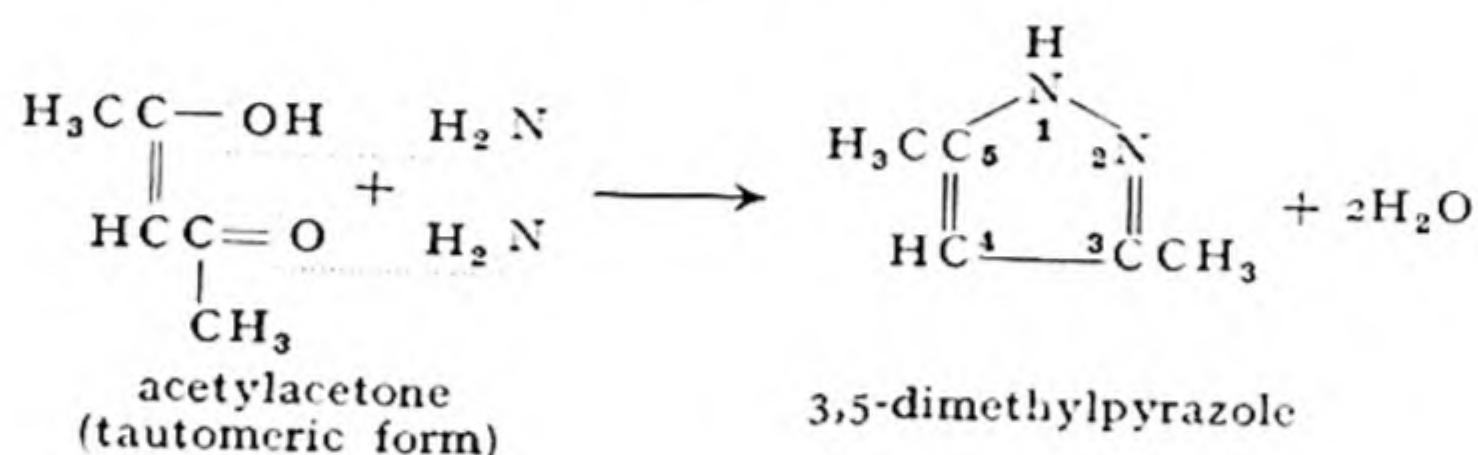
4-Aminopyrazole, which is produced by reducing 4-nitropyrazole, can be diazotised (245) like an aromatic amine; the diazonium compound couples

in the same way as aromatic diazonium compounds to give azo-dyestuffs (248).

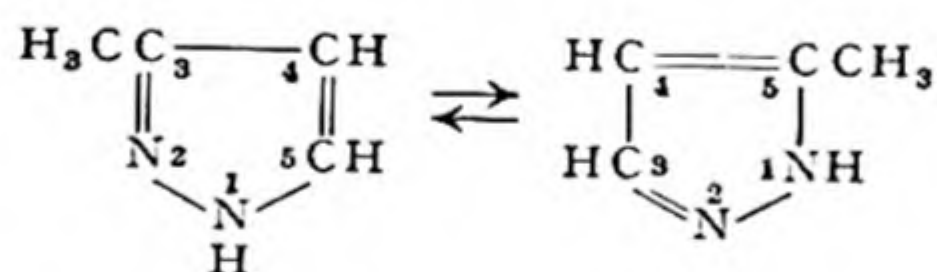
Derivatives of pyrazole are produced by the action of esters of acetylene carboxylic acids on diazoacetic ester (210) (BUCHNER):



Homologues of pyrazole can be prepared by allowing hydrazine or one of its derivatives to react with 1,3-diones (146):

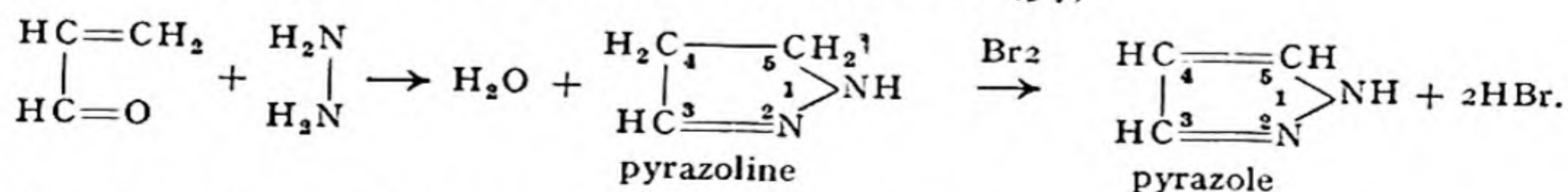


It is of theoretical importance that derivatives of pyrazole, in which a hydrogen atom in position 3 or 5 is substituted, are identical (KNORR, VON AUWERS). It must be assumed that the molecules of these compounds occur in tautomeric forms, which are interconvertible by the migration of a hydrogen atom and a change in the positions of the double bonds:



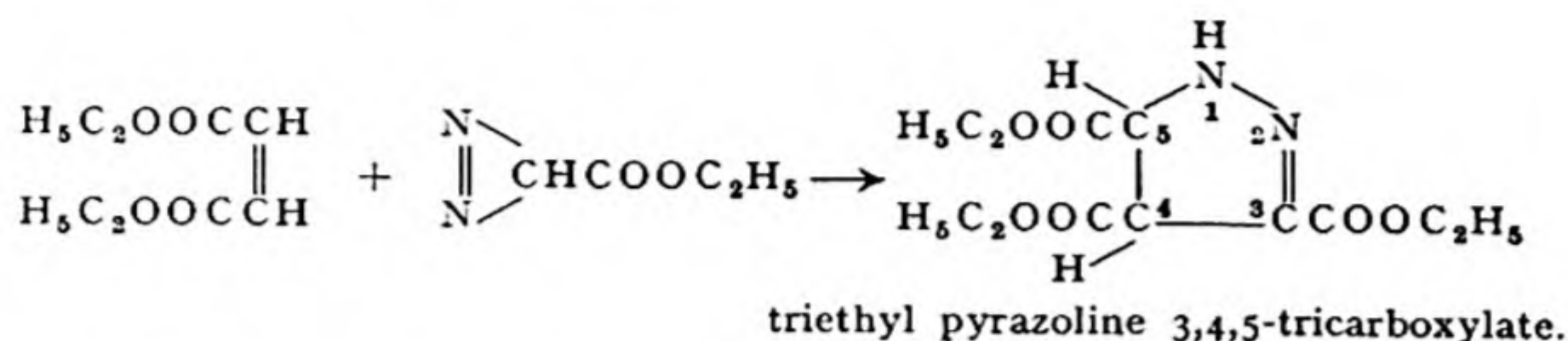
If the hydrogen atom on the nitrogen atom in position 1 is replaced by a phenyl group, two different compounds are produced, namely, 1-phenyl-3-methylpyrazole and 1-phenyl-5-methylpyrazole. When the phenyl group in these two compounds is eliminated (by oxidation), the same 3 or 5-methylpyrazole is produced from both compounds.

Several important derivatives are derived from *pyrazoline* $\text{C}_3\text{H}_6\text{N}_2$ or *dihydropyrazole*, a liquid boiling at 144° . This compound is produced by the action of hydrazine hydrate on acrolein (97):

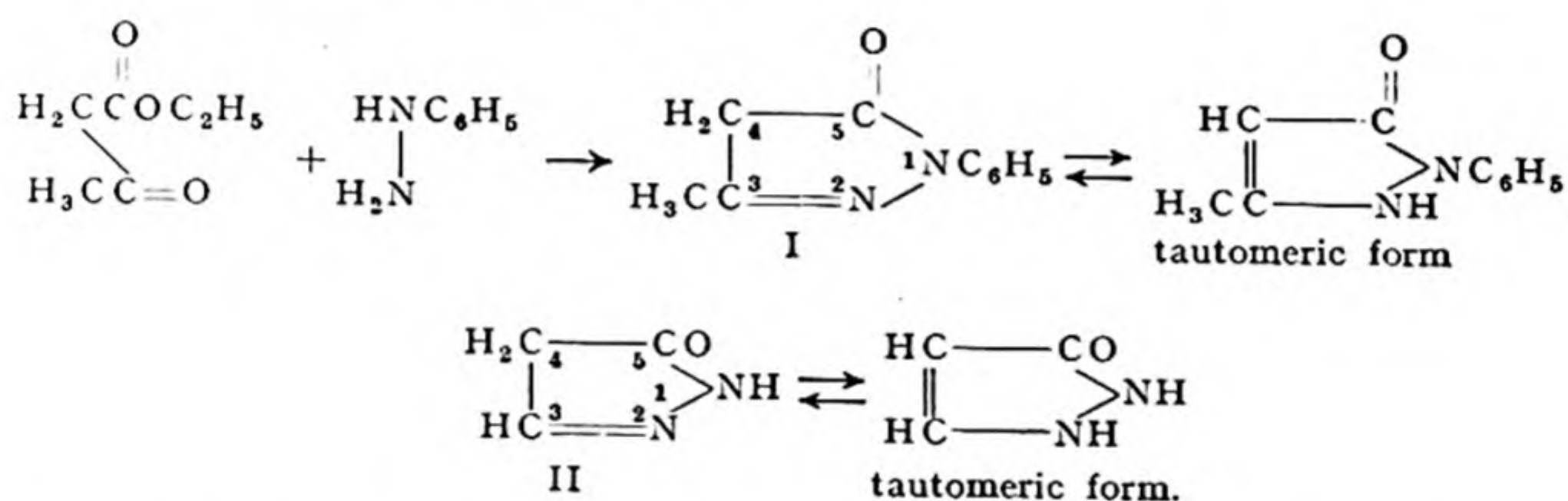


When treated with bromine, pyrazoline is converted into pyrazole, the bromine acting as a dehydrogenation agent.

Pyrazoline derivatives are also produced by the addition of ethyl diazoacetate to esters of fumaric acid:

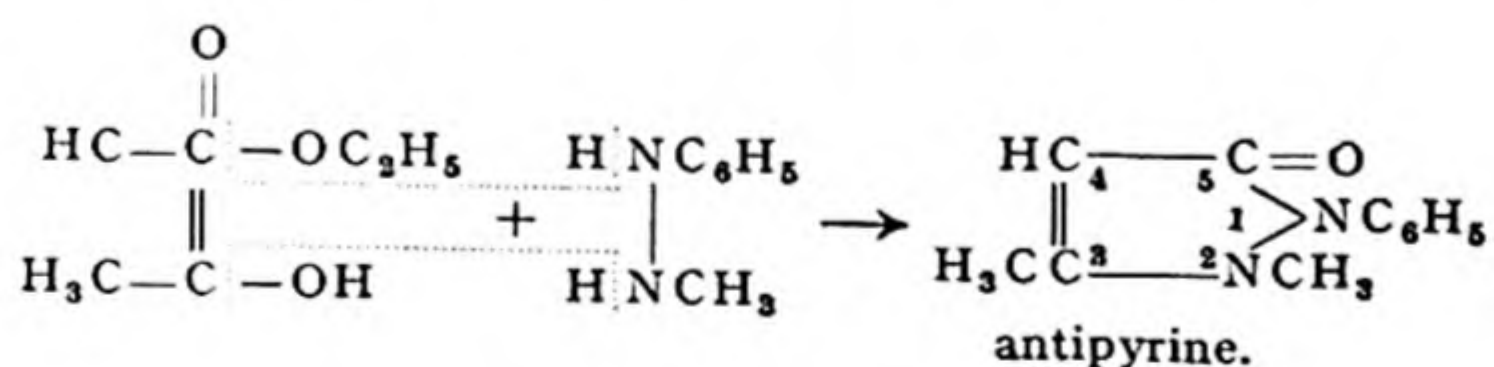


Pyrazolone $\text{C}_3\text{H}_4\text{ON}_2$, melts at 163° and sublimes at a somewhat higher temperature without decomposition. This compound (II) is a keto-derivative of pyrazoline; substituted derivatives of this compound are easily obtained from, for example, ethyl acetoacetate and phenylhydrazine, which give *1-phenyl-3-methylpyrazolone* (I) (KNORR):



The pyrazolones readily couple with diazonium salts to produce azo-dyestuffs which are of importance on account of their high light fastness.

Dimethylphenylpyrazolone $\text{C}_{11}\text{H}_{12}\text{ON}_2$ or *antipyrine* is produced by condensing ethyl acetoacetate with phenylmethylhydrazine:

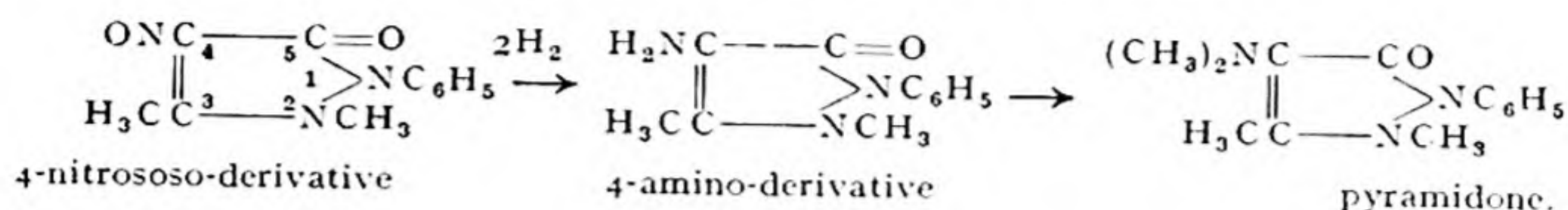


Antipyrine is prepared commercially by methylating phenylmethylpyrazolone. It is used in large quantities medicinally on account of its property as a febrifuge (KNORR 1884).

Antipyrine melts at 113° and distils in a high vacuum at 142° . It is readily soluble in water and in alcohol. The aqueous solution is coloured red by ferric chloride. A bluish green 4-nitroso-derivative is produced by the action of nitrous acid, which can be reduced to *4-aminoantipyrine*.

By methylating 4-aminoantipyrine, *4-dimethylamino-2,3-dimethyl-1-phen-*

ylpyrazolone or *pyramidone* (STOLZ) is produced, which has an even greater therapeutic action than antipyrine. It melts at 108° :



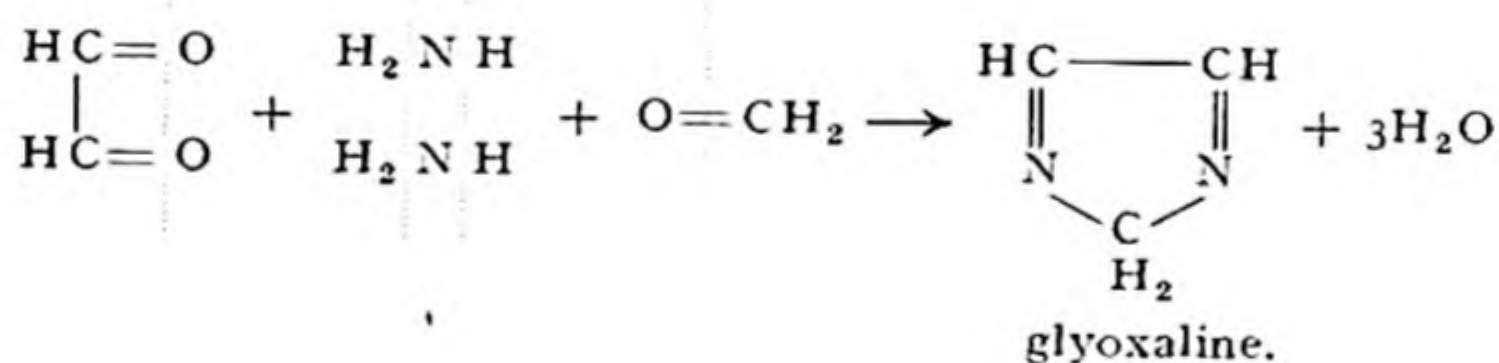
(iv) IMINAZOLE OR GLYOXALINE AND ITS DERIVATIVES

324. The iminazole ring-system is present in various important compounds occurring in living organisms.

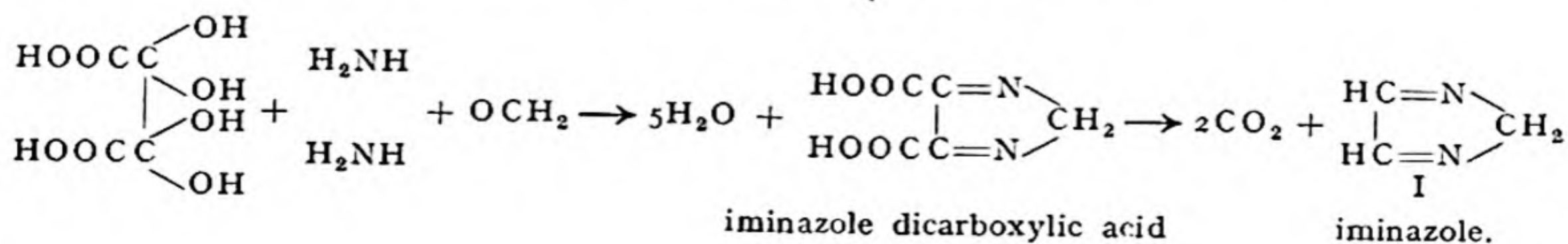
Iminazole was obtained in 1865 by DEBUS by the action of ammonia on glyoxal and was therefore called *glyoxaline*. The elucidation of its structure came later, mainly from the researches of RADZISZEWSKI and JAPP (1882). HANTZSCH suggested the name iminazole in order to bring out the relationship as regards structure with oxazole and thiazole.

Iminazole or glyoxaline $\text{C}_3\text{H}_4\text{N}_2$ melts at 90° and boils at 256° . It is very readily soluble in water and alcohol but difficultly soluble in ether; it is isomeric with and more basic than pyrazole; it forms salts which are stable in water.

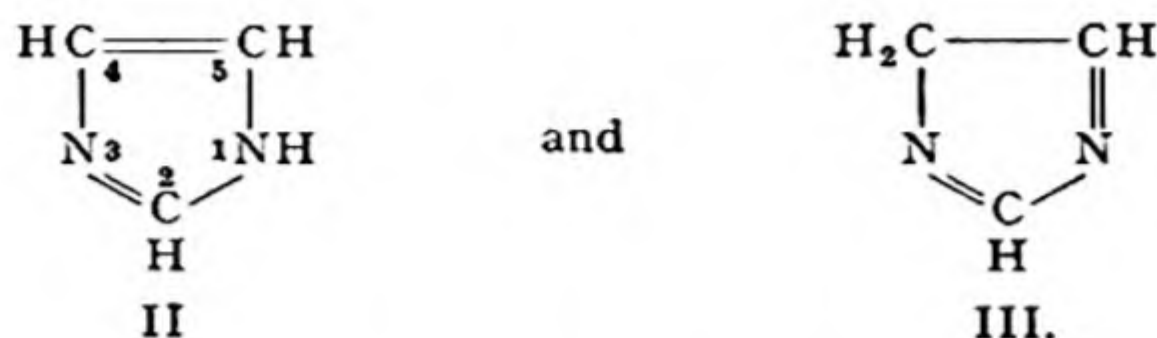
Preparation and structure of glyoxaline. A general method for preparing iminazole and its homologues consists in condensing glyoxal or a 1,2-diketone with ammonia and an aldehyde in aqueous alcoholic solution:



Glyoxaline can easily be obtained from the nitrate ester of tartaric acid, formaldehyde and ammonia (MAQUENNE). The so-called *dinitrotartaric acid* is an unstable compound, which passes over in aqueous solution into *dihydroxytartaric acid* with the elimination of nitrous acid. This compound is then converted into iminazole dicarboxylic acid, which breaks down into carbon dioxide and iminazole when heated to 300° :



According to this method of formation structure I should be assigned to iminazole. Two other methods of formulation are possible, however, namely:



N-alkylated derivatives are produced by the action of alkyl halides. From this it follows that formula II must be assigned to iminazole as I and III fail to explain this reaction. The atoms in the ring are numbered as shown in formula II.

The N-alkyl-derivatives will add on a molecule of alkyl halide; a quaternary ammonium salt is formed, which is decomposed by caustic potash with the rupture of the iminazole ring. Formic acid is produced and both the nitrogen atoms are split off in the form of primary amines. From this it follows that the quaternary salt must possess structure IV and not structure V:

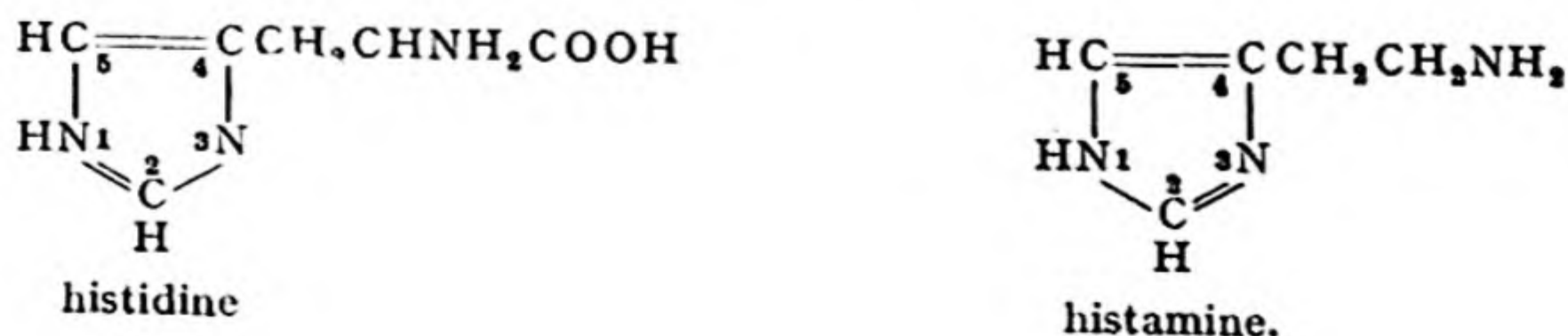


325. Derivatives of iminazole. The hydrogen attached to nitrogen is replaceable by metals. A colourless precipitate of silver iminazole $\text{C}_3\text{H}_3\text{N}_2\text{Ag}$ is produced with silver nitrate.

The C-substituted derivatives of iminazole form coloured derivatives with diazonium salts (245).

By the action of warm fuming nitric acid, iminazole is converted into a mononitro-derivative. Bromine reacts with an aqueous solution of iminazole giving 2,4,5-tribromoiminazole, which possesses acid properties and gives a silver compound; it dissolves in dilute soda solution with the formation of a sodium salt.

Histidine or 2(4'-iminazoyl)-1-aminoethane 1-carboxylic acid is an important glyoxaline derivative occurring in urine, already discussed in (199):



The structure has been established by synthesis. Histidine gives a silver salt of the composition $\text{Ag}_2(\text{C}_6\text{H}_7\text{O}_2\text{N}_3) \cdot \text{H}_2\text{O}$ and a red dyestuff with an alkaline solution of diazobenzenesulphonic acid. These reactions may be used for detecting histidine.

Histamine, *1-amino-2(4'-iminazoylethane* or β -(4-iminazoyle)-ethylamine, which has already been mentioned in 199, occurs in ergot (*secale cornutum*) (BARGER and DALE). Histamine melts at 84° and boils at 210° at 18 mms. It is produced by heating histidine to 270° when the latter compound is decarboxylated.

A condensed ring system derived from iminazole occurs in the purine derivatives (347). The iminazole ring also occurs in some alkaloids (352).

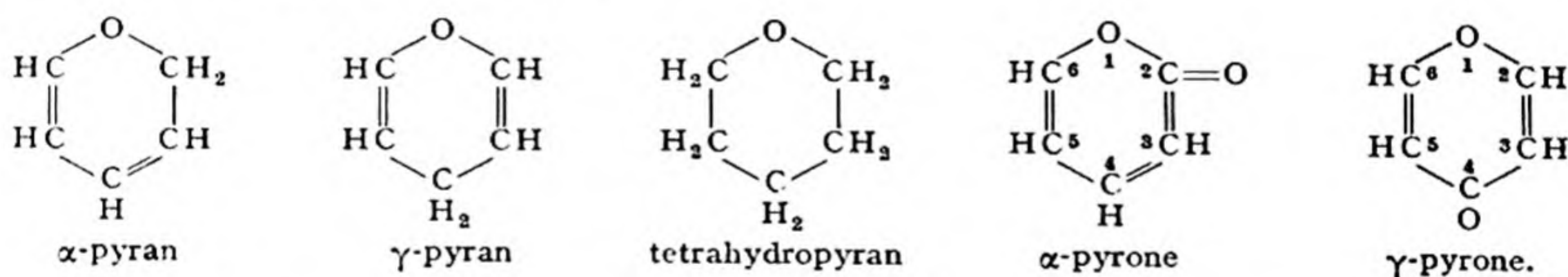
CHAPTER 13

SIX-RING SYSTEMS WITH ONE HETERO-ATOM IN THE RING

(i) PYRAN DERIVATIVES

326. A ring formed from five carbon atoms and one oxygen atom, in which two double bonds are present between carbon atoms, is named the *pyran ring*¹⁾.

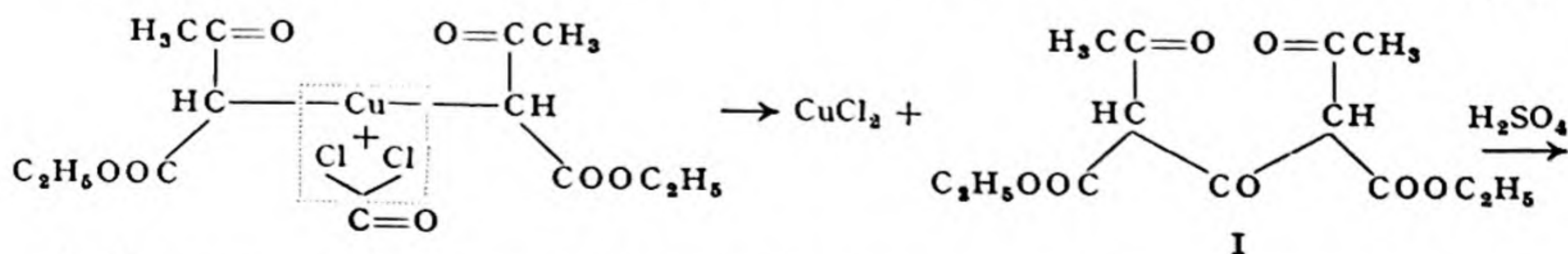
The simplest compounds containing this ring, *1,2-pyran* or α -*pyran* and *1,4-pyran* or γ -*pyran* are not yet known but their tetrahydro-derivatives are well known compounds. The anhydrides or internal ethers of 1,5-diols (111) may be considered as such.



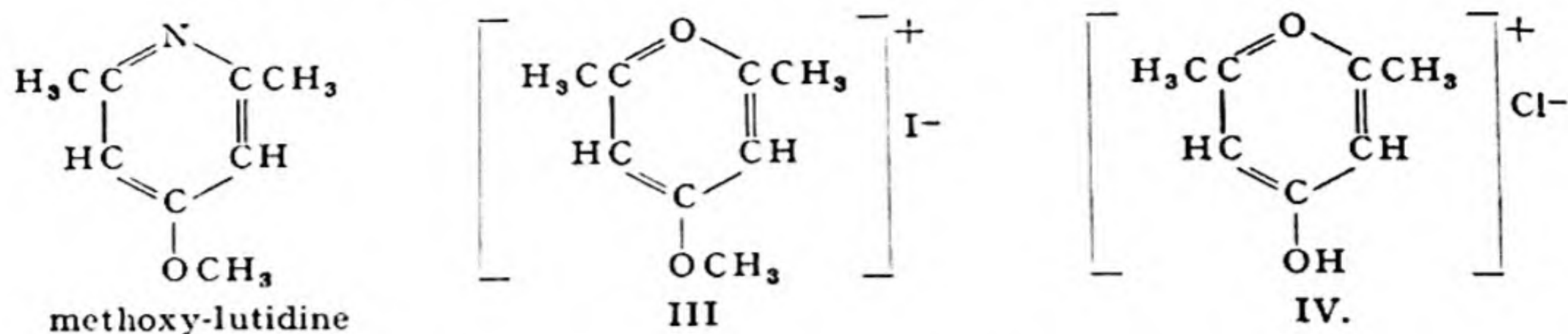
Pyrones. Numerous compounds in which a *ketopyran* or *pyrone ring* occurs, are known. *2-Ketopyran*, *1,2-pyrone* or α -*pyrone* has been obtained synthetically but is of little importance.

4-Ketopyran, *1,4-pyrone* or γ -*pyrone* is not itself known but several of its derivatives are of great importance from a theoretical standpoint.

Derivatives of γ -pyrone. *2,6-Dimethyl- γ -pyrone* (IV) can be prepared from the copper compound of ethyl acetoacetate (148) and carbonyl chloride (150):



¹⁾ The nomenclature "pyranoid sugars" for saccharides with a ring system of five carbon atoms and one oxygen atom (160) is not in accordance with the definition given above. Actually these sugars ought to be designated as derivatives of tetrahydropyran. The term "pyranoid" is in general use however as an abbreviation.



In formulae III and IV the distribution of the valency bonds is different from that of the bonds in γ -pyrone. The ring-system occurring in III and IV, in which the distribution of the valency bonds is the same as in a benzene ring, is called a *pyroxonium* or *pyrylium ring*. The salts of dimethylpyrone are then called *pyroxonium* or *pyrylium salts*.

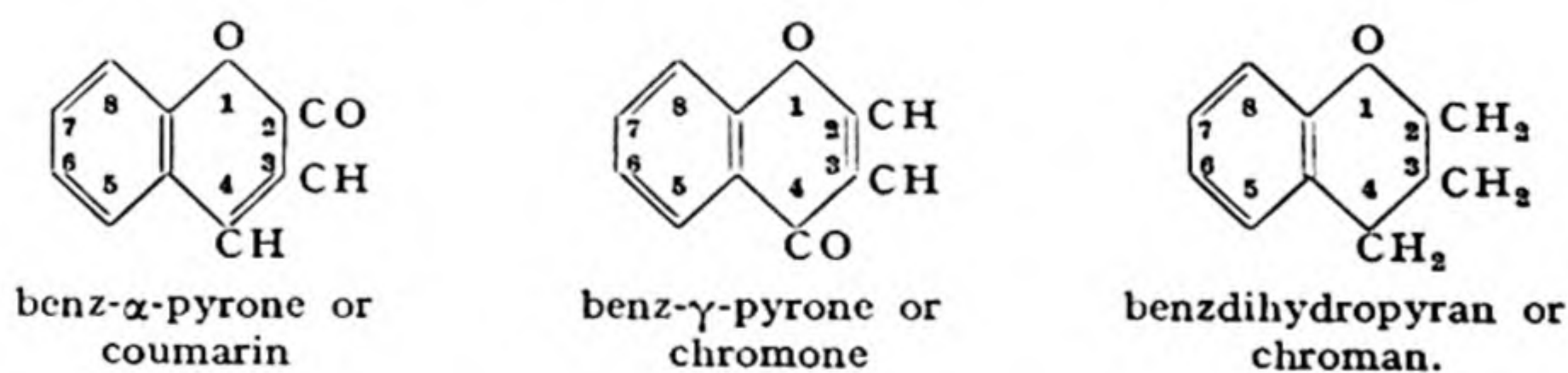
Derivatives of benzpyran

327. By *benzpyran* is understood a ring-system consisting of a benzene ring condensed with a pyran ring. The benzpyrans themselves are not known but many of their derivatives are well-known compounds.

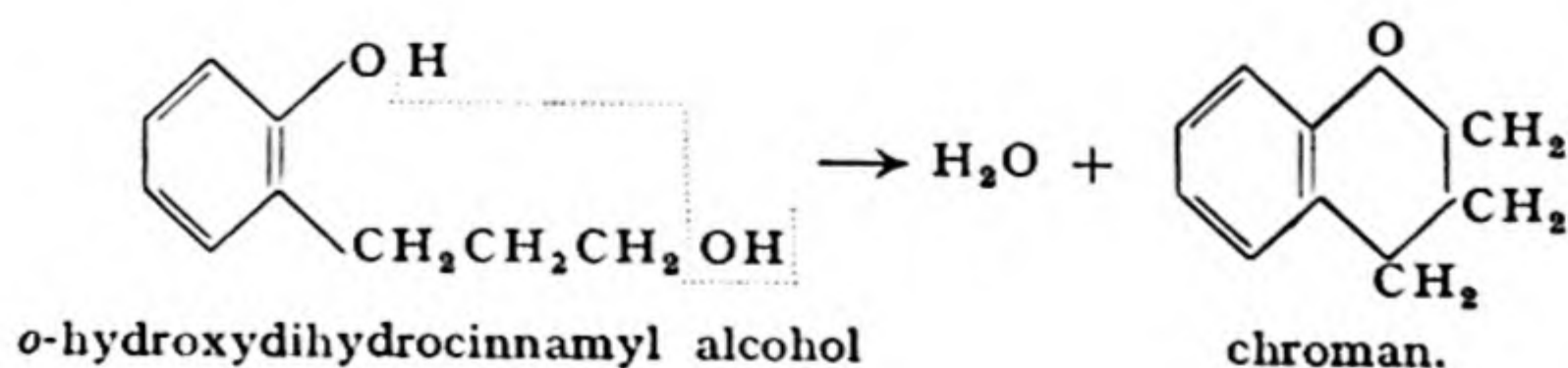
Benz- α -pyrone is coumarin which has already been discussed in 269.

Benz- γ -pyrone is called *chromone* because this atomic grouping occurs in the vegetable dyestuffs, the *flavones* (328).

A compound in which a benzene ring is condensed with a hydrogenated γ -pyran ring, *i.e.* *benzdihydropyran*, is called a *chroman*:

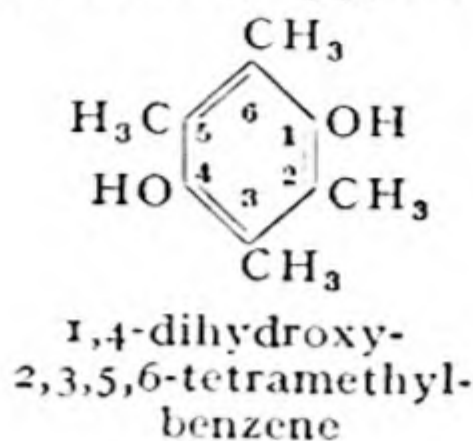


Chroman is readily produced from *o*-hydroxydihydrocinnamyl alcohol by eliminating water:

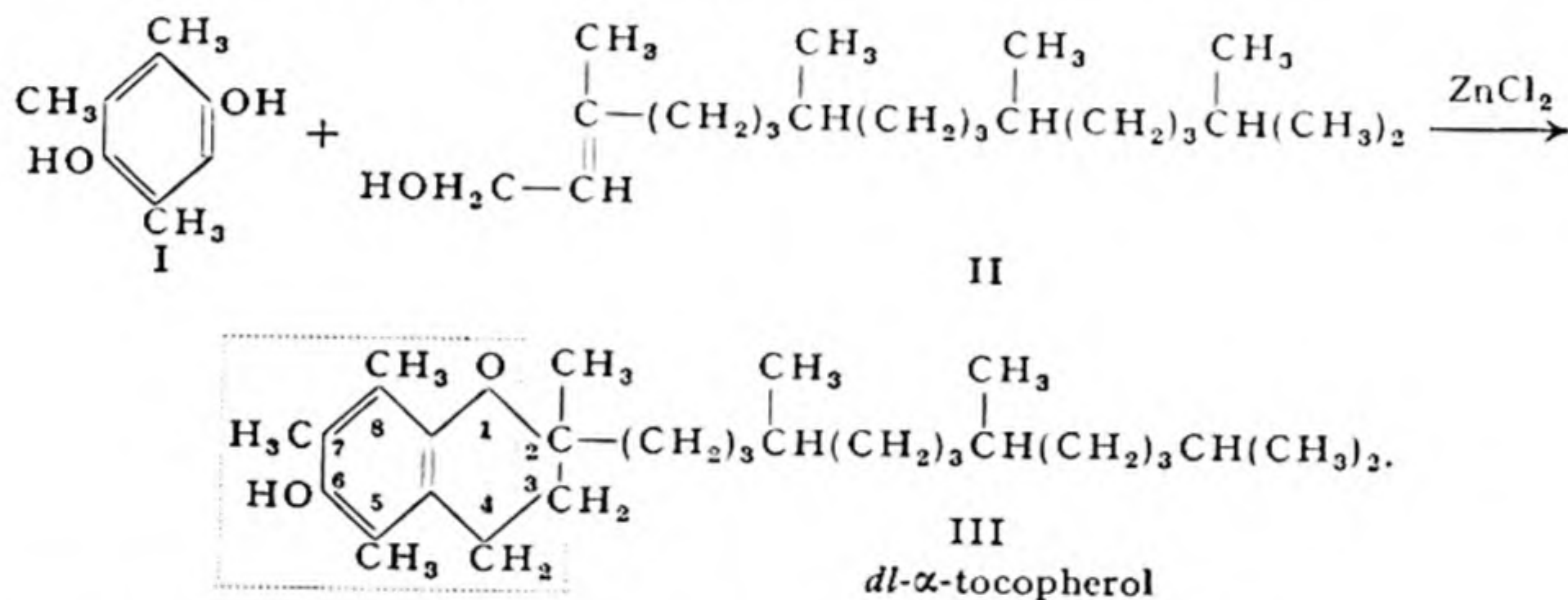


The structure of vitamin-E or α -tocopherol (III), (306), has been elucidated mainly by E. FERNHOLZ, A. R. TODD, P. KARRER and their collaborators. 1,4-Dihydroxy-2,3,5,6-tetramethylbenzene or tetramethylhydroquinone is produced by the thermal decomposition of α -tocopherol, $C_{29}H_{50}O_2$.

This group of atoms is shown by a dotted line in formula III. By heating 2,5,6-trimethylhydroquinone (I) with phytol (II) (95) in solution in decalin in the presence



of zinc chloride as a condensing agent, a compound is produced, which is very similar in chemical and physiological properties to natural α -tocopherol and is therefore considered to be *dl*- α -tocopherol (III):



This synthesis is not a strict proof of the presence of a chromane ring; other arguments can be brought forward however but it is not possible to go into them in this book.

Synthetic α -tocopherol is racemic with respect to carbon atom 2.

Flavones

328. The colours of yellow flowers, roots and various kinds of woods are produced by colouring matters belonging to various classes. Yellow pigments of the carotenoid group have already been discussed in 308. Another group the *flavones* (derived from *flavus* = bright yellow), which occur very widely distributed in nature, are derivatives of flavone, which may be considered as the parent of this group.

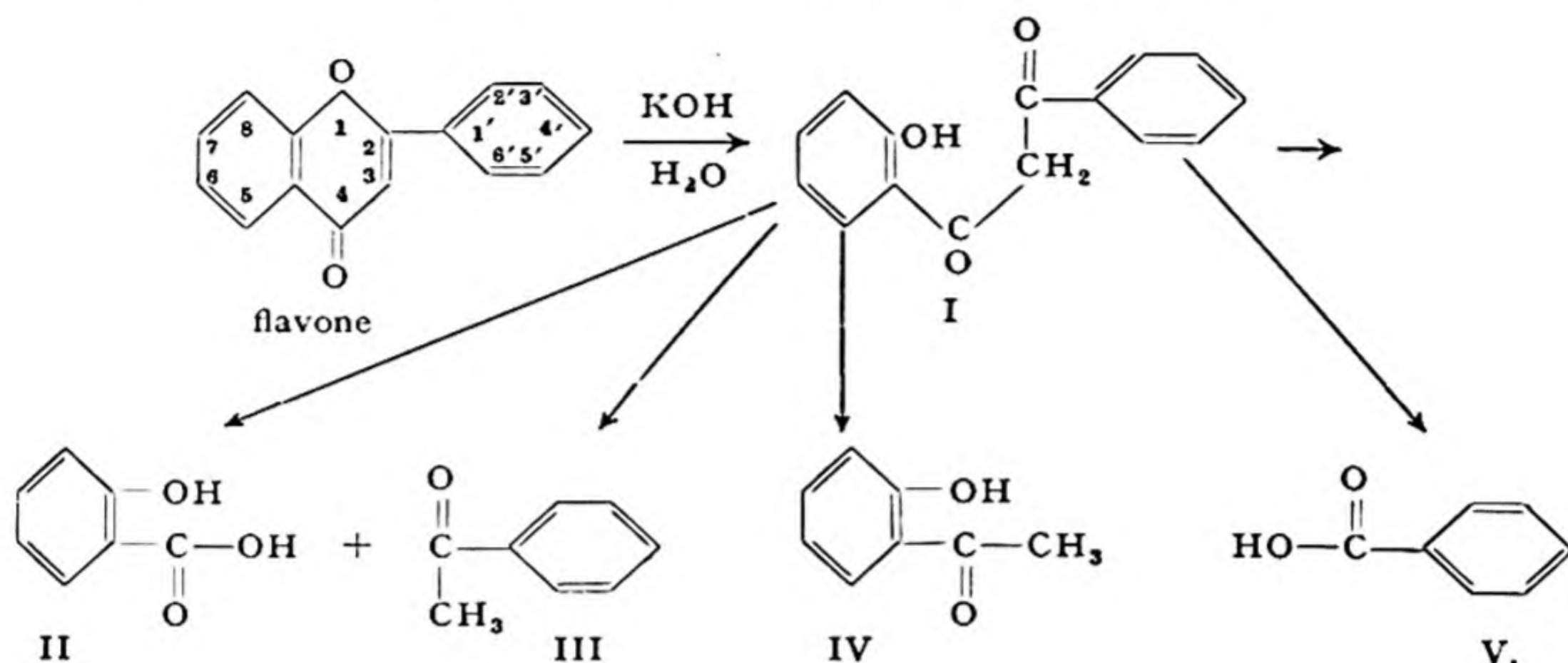
These colouring matters occur in plants in the form of glucosides (179) combined with *d*-glucose or *l*-rhamnose (163); sometimes they occur in the uncombined state.

The flavones were investigated at the beginning of this century by v. KOSTANECKI, who worked out several syntheses for compounds of this group; later on A. G. PERKIN carried out some important researches in this field.

Flavone $C_{15}H_{10}O_2$, a colourless compound melting at 100° , which is very sparingly soluble in water but readily soluble in alcohol, occurs in the veget-

able kingdom as a white deposit on the leaves and flower stalks of various kinds of primula.

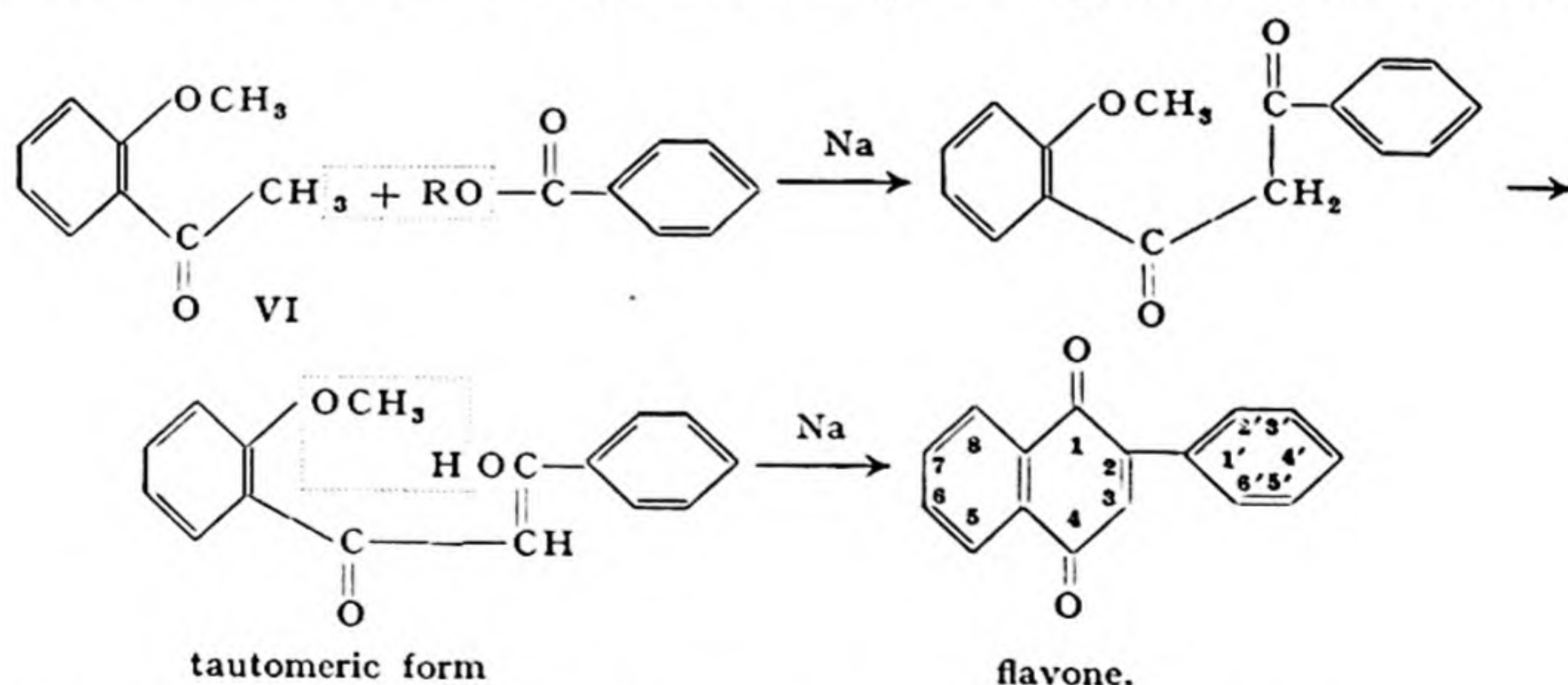
The *structure of flavone* follows from the way this compound is decomposed with alkali. *o*-Hydroxydibenzoylmethane (I) is first produced, which then breaks down further giving salicylic acid (II) and acetophenone (III) along with benzoic acid (V) and *o*-hydroxyacetophenone (IV):



Hence flavone is *2-phenylbenz-γ-pyrone* or *2-phenylchromone*.

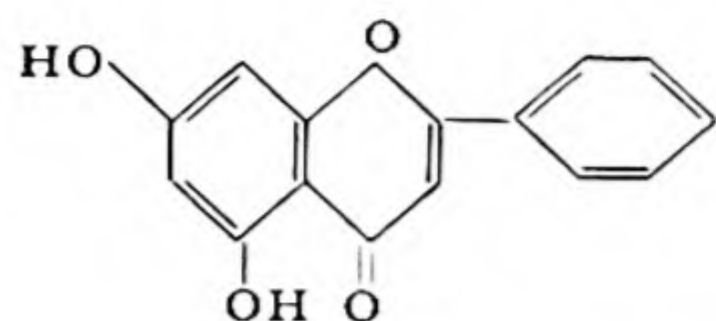
Flavones can be prepared synthetically by a general method consisting of the condensation of *o*-methoxyacetophenone (VI) or one of its derivatives with an ester of an aromatic acid with the aid of sodium.

Thus for flavone itself the synthesis may be represented as follows:

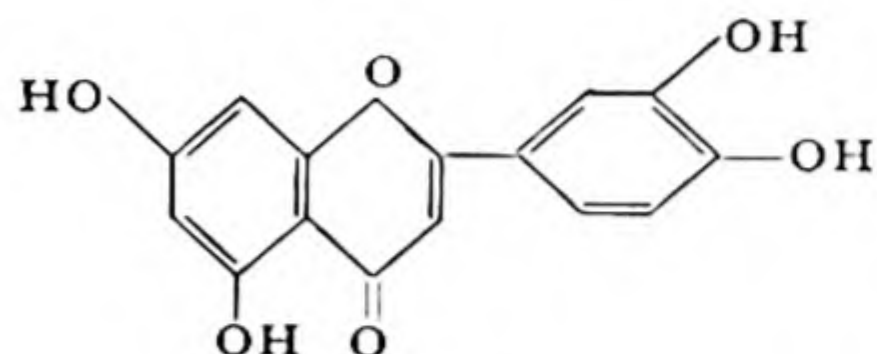


The colouring matters derived from flavone contain hydroxyl groups on carbon atoms 5 and 7 and sometimes on carbon atoms 3', 4' or 5'. Compounds also occur with methoxyl groups in place of some of the hydroxyl groups. The structure of the various flavones follows from the degradation products, which are formed by heating with alkali; thus 1,3,5-trihydroxybenzene and 3,4-dihydroxybenzoic acid are produced from *quercetin* (v. KOSTANECKI).

In a number of cases the structure has been confirmed by synthesis. Some of these compounds are mentioned below.

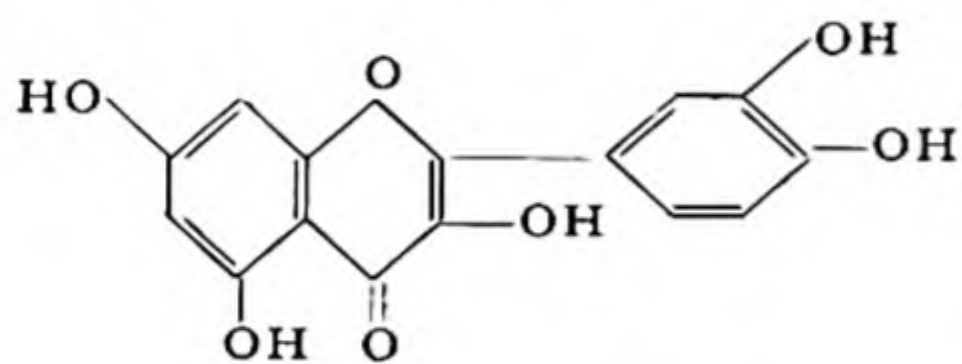


Chrysin $C_{15}H_{10}O_4$, m.p. 275° , occurs in poplar buds.

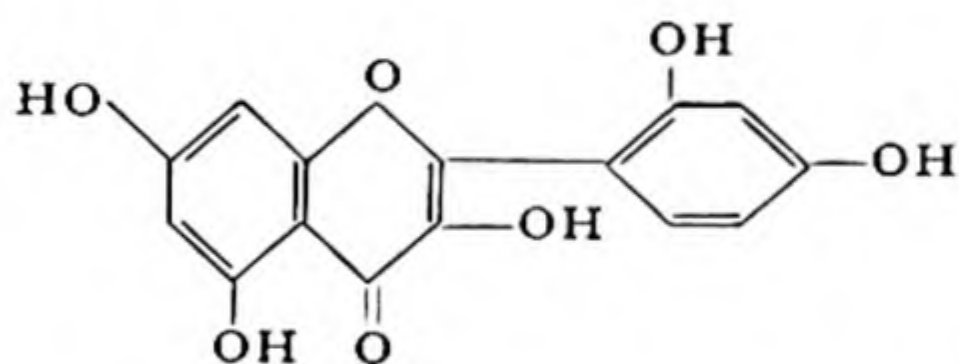


Luteolin $C_{15}H_{10}O_6$, m.p. 329° , occurs in weld (*reseda luteola*).

329. Flavonols. Some yellow vegetable dyestuffs, which are included in the flavone group, are derivatives of *flavonol* or *3-hydroxyflavone*. The following are mentioned as examples:



Quercetin $C_{15}H_{10}O_7$, m.p. 314° , occurs in the form of a rhamnoside in the bark of the American oak (*quercus tinctoria*) and in horse chestnut leaves.



Morin $C_{15}H_{10}O_7$, m.p. 290° , occurs in a yellow wood, old fustic (*chlorophora tinctoria*, Gaudich).

The colouring matters belonging to the flavones and flavonols are yellow, crystalline compounds, which are soluble in dilute alkalis on account of the presence of phenolic hydroxyl groups and in dilute acids because they can form oxonium salts. The latter are decomposed by water.

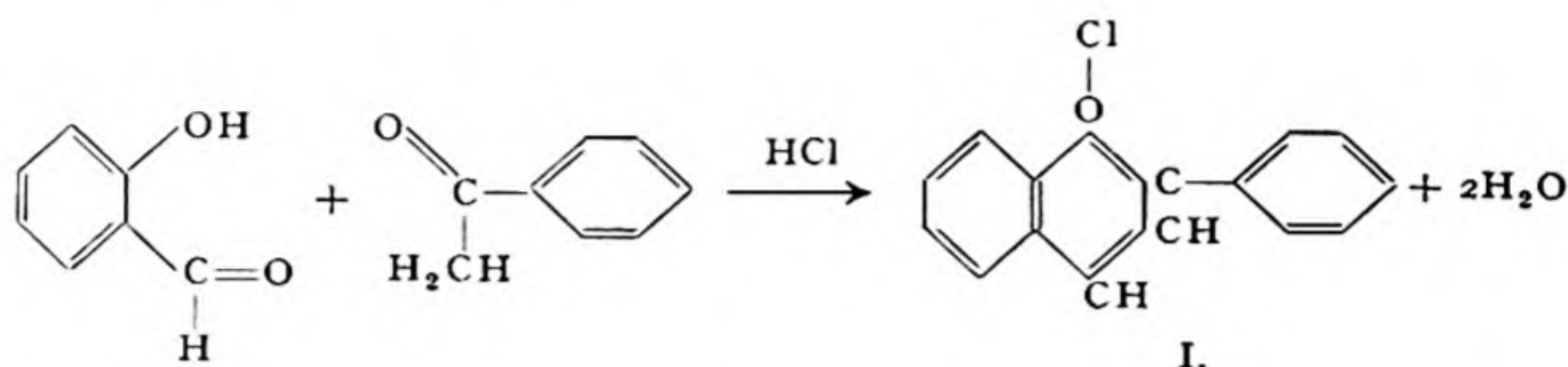
Luteolin was at one time an important dyestuff; quercetin and morin (quercitrin bark and old fustic) are still used as mordant dyestuffs (252, 283). The colouring matters in brazilwood (American species of *caesalpinia*) and logwood (*haematoxylon campechianum*) used in dyeing, are related to the flavonols.

Benzpyroxonium compounds

330. A number of compounds are known in which a benzene ring is condensed with a *pyroxonium* or *pyrylium* ring. These compounds have the properties of oxonium salts. They can form salts on account of their basic character.

The benzpyroxonium or benzpyrylium grouping has a similar structure to the pyrylium grouping in salts of dimethyl- γ -pyrone (326).

2-Phenylbenzpyroxonium or *2-phenylbenzpyrylium chloride*, which is known also as *flavylium chloride* (I), was obtained by DECKER and von FELLEBERG by condensing salicylaldehyde and acetophenone in alcoholic hydrochloric acid:



This yellow salt is very hygroscopic and decomposes in air. It gives a stable yellow double salt, $C_{15}H_{11}OCl \cdot FeCl_3$, with ferric chloride. The oxonium base derived from I is very unstable and has not been obtained in a pure state.

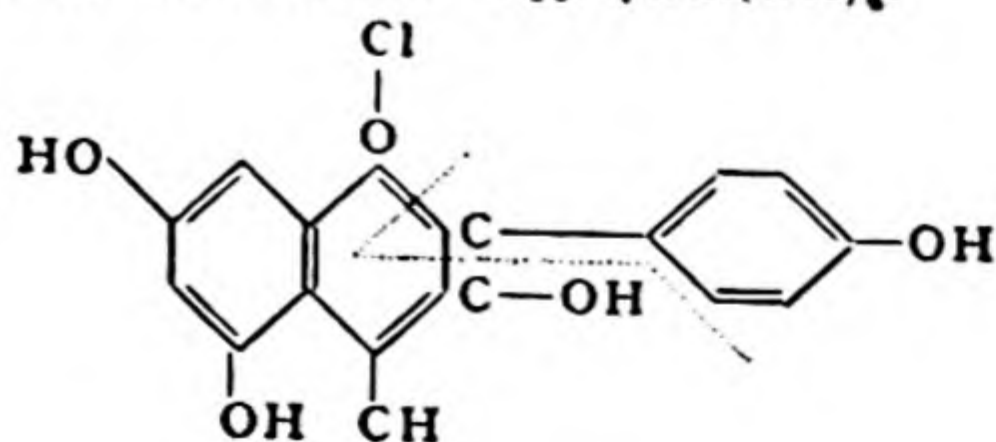
Anthocyanins and anthocyanidins

331. The blue, purple, violet and red colours of flowers and fruits are caused by colouring matters dissolved in the sap, to which the name *anthocyanins* (derived from greek words for flower and blue) was given long before their structure was known. Our knowledge of the chemical composition of these colouring matters is due in the first place to WILLSTÄTTER (1913) and later on important researches in this field were carried out by P. KARRER, Sir ROBERT and G. M. ROBINSON. These colouring matters are glucosides, so that they are now known as *anthocyanins* or *anthocyanosides*.

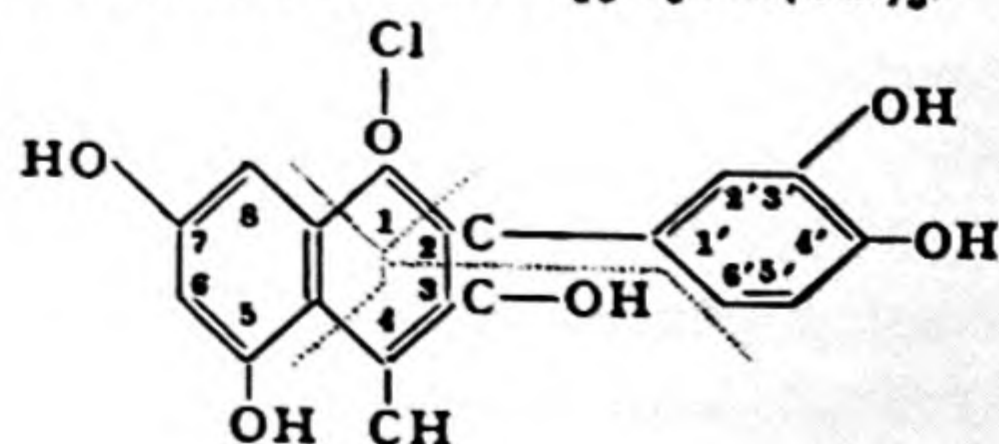
By heating for a short time with dilute mineral acids, one or more, usually two molecules of a monosaccharide (*d*-glucose, *d*-galactose, *l*-rhamnose) are split off with the production of the free colouring matters. The latter are called *anthocyanidins*.

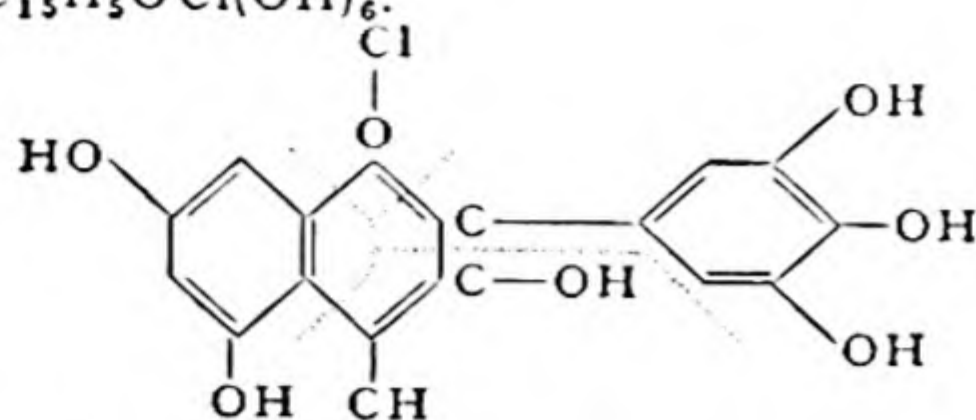
It has been found that all the anthocyanidins contain the flavylium grouping (330). The three fundamental types are as follows:

I. Pelargonidin chloride $C_{15}H_7OCl(OH)_4$.



II. Cyanidin chloride $C_{15}H_6OCl(OH)_5$.



III. Delphinidin chloride $C_{15}H_5OCl(OH)_6$ 

These structures follow from the fission products obtained from these compounds by fusion with alkali. Phloroglucinol (232) is produced from all three. The second fission product is *p*-hydroxybenzoic acid from I, protocatechuic acid from II and gallic acid (263) from III. The formation of these fission products is indicated in the above formulae by dotted lines. The structures have been confirmed by synthesis (P. KARRER, R. ROBINSON). Other anthocyanidins carry methoxyl groups in place of hydroxyl groups on one or more of carbon atoms 3', 4' or 5'.

In the simplest anthocyanins the monosaccharide residue is attached to carbon atom 3. KARRER was able to demonstrate this by methylating the anthocyanin and determining the position of the free hydroxyl group in the methylated cyanidin obtained after removing the sugar residue by hydrolytic fission.

In the diglucosides, the second glucose residue is attached to carbon atom 5. ROBINSON has prepared the colouring matter of wild mallow, *malvin chloride*, synthetically, it contains two glucose residues on atoms 3 and 5, two methoxyl groups on 3' and 5' and two hydroxyl groups on 7 and 4'.

The anthocyanins are soluble in water, methanol and ethanol and insoluble in ether, benzene and chloroform. In order to isolate these colouring matters from plants, the material is extracted with ethanol or methanol containing hydrogen chloride. On the addition of ether, the readily crystallisable chloride (oxonium salt) is precipitated and may be purified by recrystallisation from alcoholic hydrochloric acid.

Since anthocyanins contain phenolic hydroxyl groups, they are soluble in alkalis; thus these colouring matters are amphoteric in character. The oxonium salts are usually red in colour and the phenates blue. The blue colour of the cornflower is due to the potassium, sodium, ammonium or calcium salt of the same colouring matter, which produces, as an oxonium salt, the red colour of the light red variety of red roses and red dahlias, namely, cyanin, *i.e.* the diglucoside of II. This substance is red in solutions having $p_H = 3.0$ or less, violet at $p_H = 8.5$ and blue at $p_H = 11.0$. The precise structure of the colour base, which is present at $p_H = 8.5$, is not yet known with certainty.

The anthocyanidins show strong selective absorption (13, 251) in the region of 6000-2000 Å. The maximum absorption lies in the visible spectrum and there is also

an absorption band at 2700 Å. The extinction curve for a particular anthocyanidin is approximately the same as that for the corresponding anthocyanin. From this it follows that the colour of these compounds is determined by the flavylum part of the molecule.

About twenty anthocyanins have been isolated from various plants. As a rule one particular plant contains a mixture of anthocyanins.

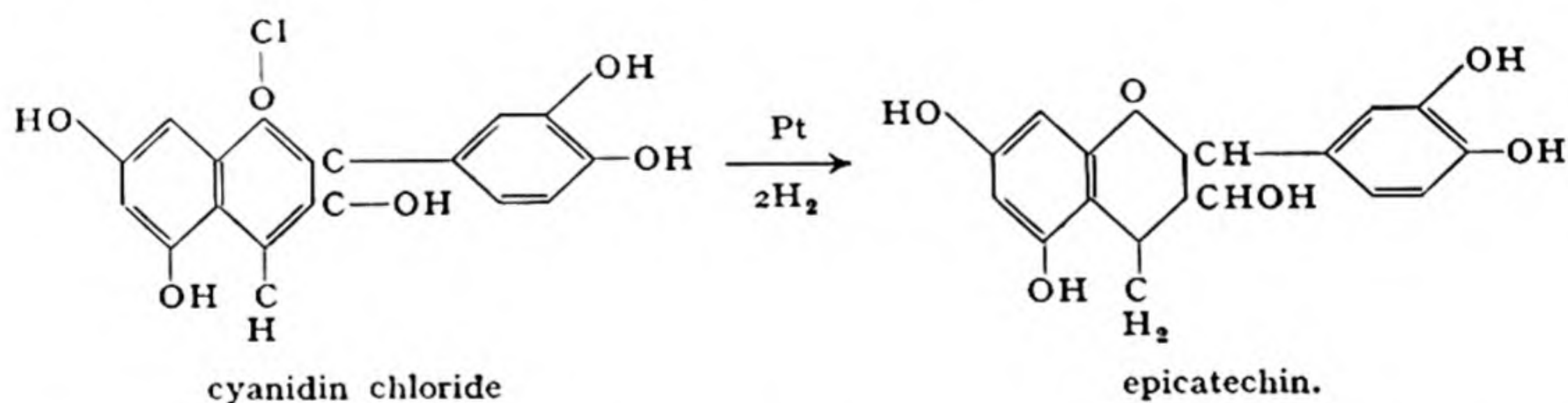
The petals of the blue cornflower contain 0.75 % of cyanin, those of some deep red dahlias contain 20 % of this colouring matter and those of the dark blue viola even 30 % (all calculated on dry petals) in the form of various salts.

Pelargonin, the diglucoside of pelargonidin, is the colouring matter present in red pelargonium and orange-red dahlias. *Delphinin*, a diglucoside of delphinidin, is the colouring matter in *delphinium consolida* and *violanin*, a rhamnoglucoside of delphinidin occurs in *viola tricolore*.

From the structural formulae of the anthocyanidins and the flavonols, it appears that the latter may be regarded as oxidation products of the former. Possibly in the plant, colouring matters of either class may be converted into one another by oxidation or reduction. This has been accomplished chemically in the case of quercetin (329), which is converted into cyanidin by reduction with magnesium and hydrochloric acid.

Catechins. These compounds are crystalline colouring matters and occur in many kinds of plants. They are to be considered as hydrogenated derivatives of flavonols or anthocyanidins.

1-*Epicatechin* from *acacia catechu* is a chroman derivative (327), as appears from the formation of *dl*-epicatechin by the catalytic reduction of cyanidin chloride (FREUDENBERG):



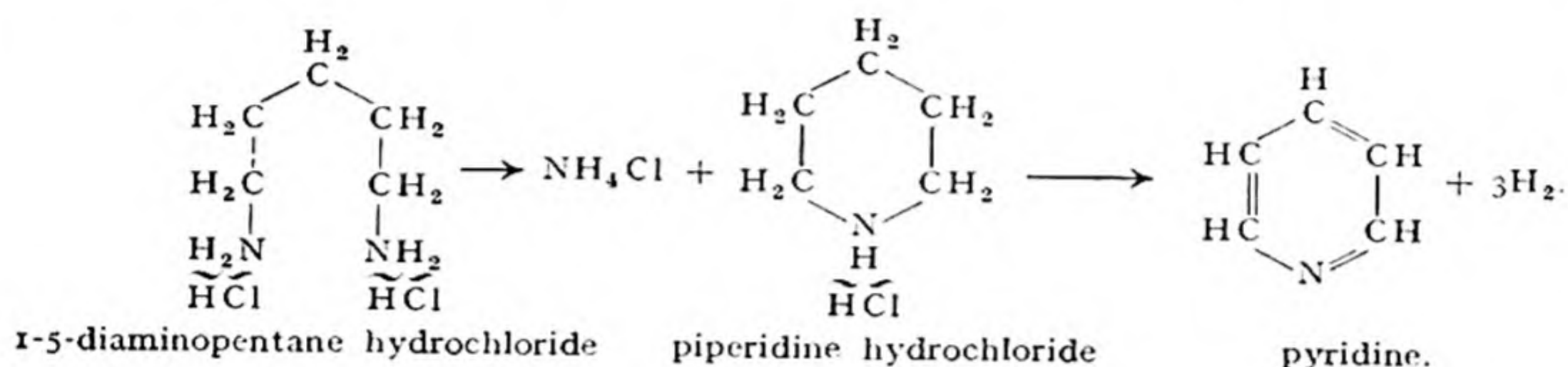
The catechin from gambir (264) is probably stereoisomeric with epicatechin.

(ii) PYRIDINE AND ITS DERIVATIVES

332. *Pyridine* C_5H_5N was discovered by ANDERSON in 1850 in "bone-oil" (314), and soon after, some of its derivatives were found in the decomposition products obtained by heating cinchonine (358) with potash. Pyridine occurs along with some of its homologues in coal-tar. It is a colourless liquid, with a spec. grav. of 1.0031 at 0°, a boiling point of 115.5° and a melting point of -41.5°. It is miscible with water in all proportions, and possesses weakly basic properties; the aqueous solution reacts neutral towards litmus. It has an unpleasant odour.

Preparation of pyridine. Commercially pyridine is recovered from coal-tar. To this end the light oil fraction (219) is extracted with sulphuric acid, which removes the pyridine bases as soluble sulphates. Soda is then added to the aqueous acid solution and a dark brown basic liquid separates, from which pyridine and its homologues are obtained by fractional distillation.

Structure of pyridine. This follows from the following synthesis. On heating the hydrochloride of 1,5-diaminopentane, piperidine (117) is produced and this compound can then be converted into pyridine in various ways, *e.g.* by passing it over heated platinum or palladium at 250° by which hydrogen is split off or by heating with concentrated sulphuric acid, which acts as an oxidising agent:



It may be assumed therefore that the same closed ring of atoms, consisting of five carbon atoms and one nitrogen atom, occurring in piperidine, occurs also in pyridine. This assumption is confirmed by the formation of pyridine from quinoline (337). Since pyridine has the characteristics of a tertiary amine, which is shown by the direct addition of methyl iodide, the nitrogen atom in pyridine carries no hydrogen atoms.

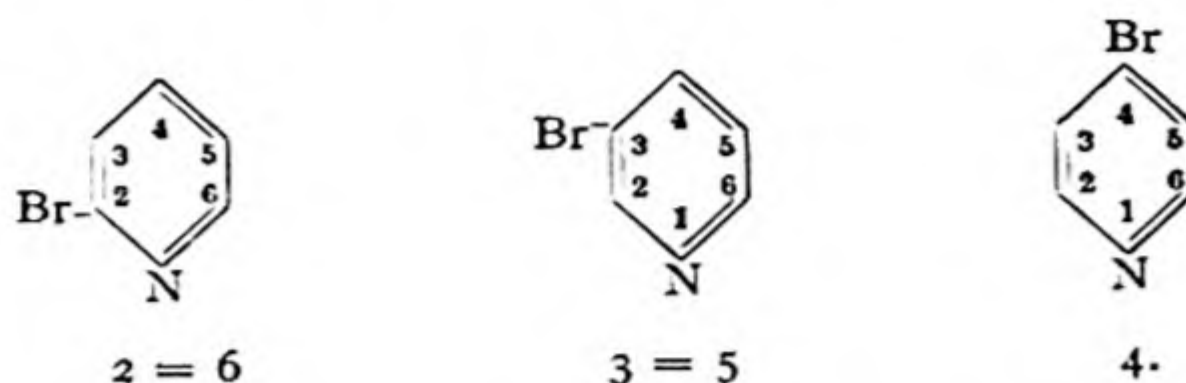
By analogy with the structure of benzene, KÖRNER (1869) and DEWAR (1871) assumed the presence of alternate double and single bonds in the six-ring of pyridine. Subsequently it was found that in chemical properties, pyridine strongly resembles benzene.

By the action of ozone on 2,3-dimethylpyridine or on 3,4-dimethylpyridine and decomposition of the reaction product with water, glyoxal, methylglyoxal and dimethyl glyoxal are formed (WIBAUT and KOOYMAN). From this it follows that these dimethylpyridines can react according to the following two valency structures:

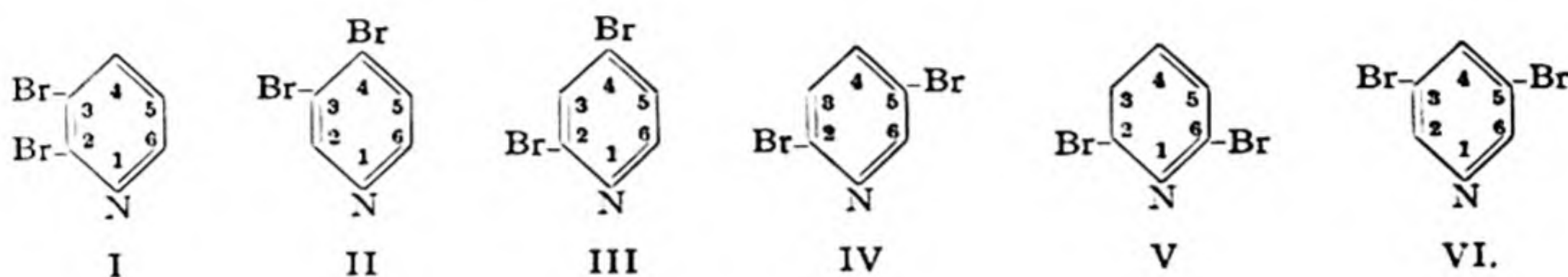


In agreement with this fact it is assumed that the pyridine molecule is also a mesomeric form.

From the above structure for the pyridine ring it follows that three mono-substitution products are to be expected, viz. 2 = 6, 3 = 5 and 4:



With identical substituents, six disubstituted products are to be expected, viz. 2,3 = 6,5; 3,4 = 5,4; 2,4 = 6,4; 2,5 = 6,3; 2,6 and 3,5. This agrees with the experimental results:

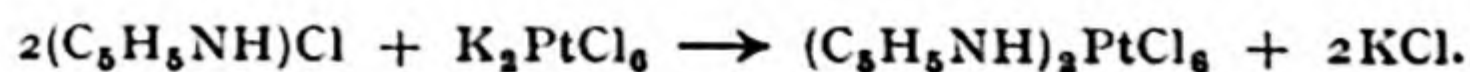


The orientation of pyridine derivatives is more complicated than with benzene derivatives. On introducing a second substituent into a pyridine derivative already carrying a substituent in position 2, theoretically four isomeric disubstitution products can be produced, viz. I, III, IV and V. The same applies to the introduction of a second substituent into pyridine substituted in the 3-position, when I, II, IV and VI are produced. Only two isomers can be formed by introducing a second substituent into a pyridine derivative substituted in position 4.

Hence, theoretically, it should be possible to decide whether one is dealing with a pyridine derivative substituted in the 4-position or with one carrying a substituent in either position 2 or position 3. Since, experimentally, the introduction of substituents into pyridine derivatives is in many cases very difficult and in some cases even impracticable, this method of orientation is seldom used. The carboxylic acids, which are produced from the homologues of pyridine, serve as the basis for orientation in this series. For this reason the homologues will be discussed before the products of substitution.

Chemical properties of pyridine. With acids pyridine forms salts which are usually readily soluble in water, the picrate, which can be used for purifying pyridine, is an exception however.

The hydrochloride and other salts give double salts with various inorganic salts, *e.g.*:



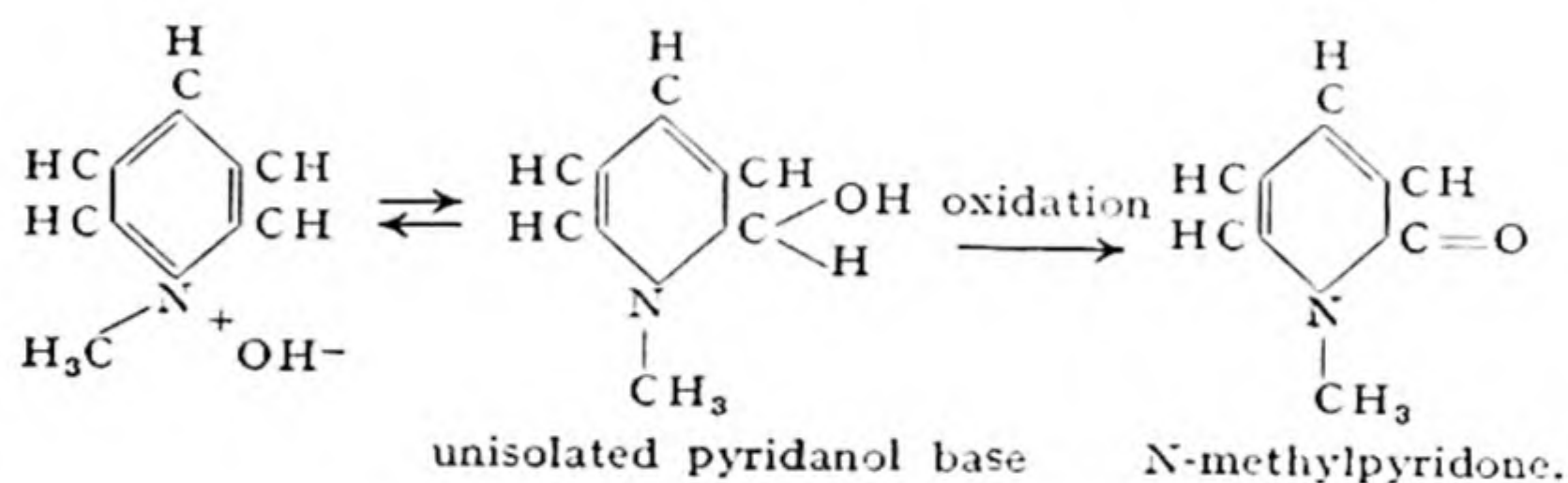
This chloroplatinate, as well as the double salts with mercuric chloride or ferrocyanide, may be used for precipitating pyridine and in this way isolating it.

Pyridine is stable towards oxidising agents. It is not attacked by either alkaline permanganate, chromic acid or even boiling nitric acid.

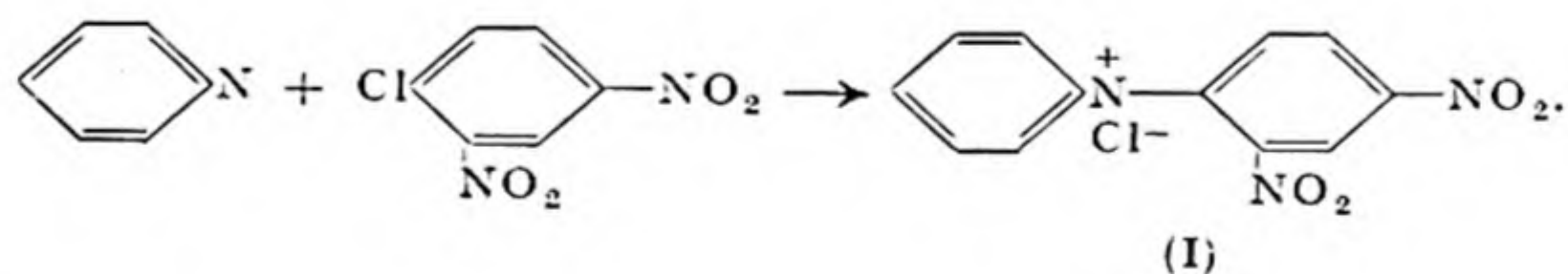
When pyridine is warmed with methyl iodide, *pyridine methiodide* ($C_5H_5NCH_3$)I, is produced. In this addition product, as in other ammonium iodides, the iodine atom may be replaced by hydroxyl by treatment with moist silver oxide with the formation of a *quaternary pyridinium base*.

If a solution of methylpyridinium iodide is made alkaline and then oxidised either electrolytically or with potassium ferricyanide, *N-methylpyridone* is produced (DECKER).

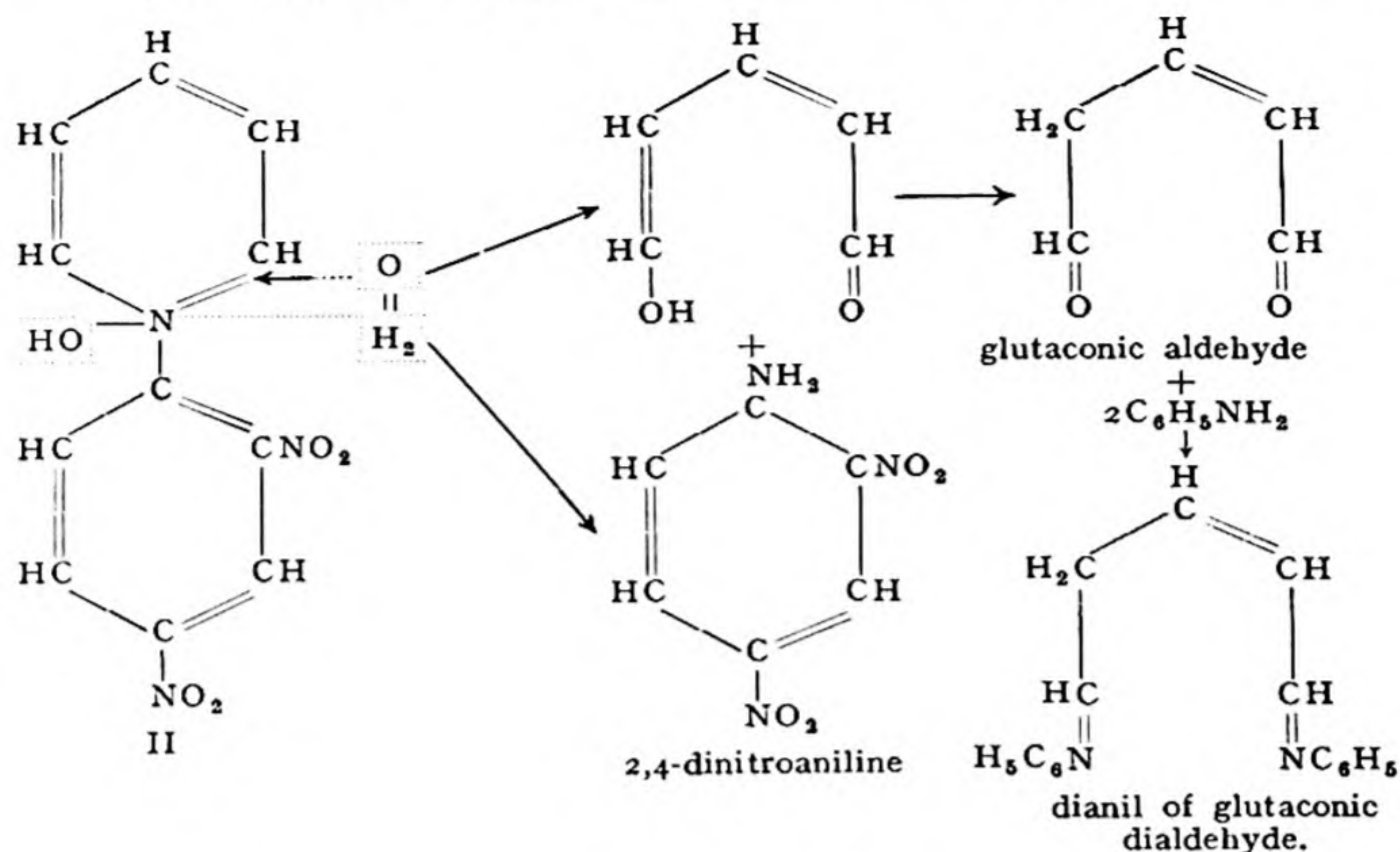
It is assumed that the methylpyridinium base is converted into a tautomeric form, the *pyridanol base*, which then forms the pyridone on oxidation:



A very remarkable reaction by which the pyridine ring is opened, was discovered by ZINCKE. Pyridine is warmed with 1-chloro-2,4-dinitrobenzene (222) to form crystalline *2,4-dinitrophenylpyridinium chloride* (I), since the chlorine atom in 1-chloro-2,4-dinitrobenzene is very reactive:

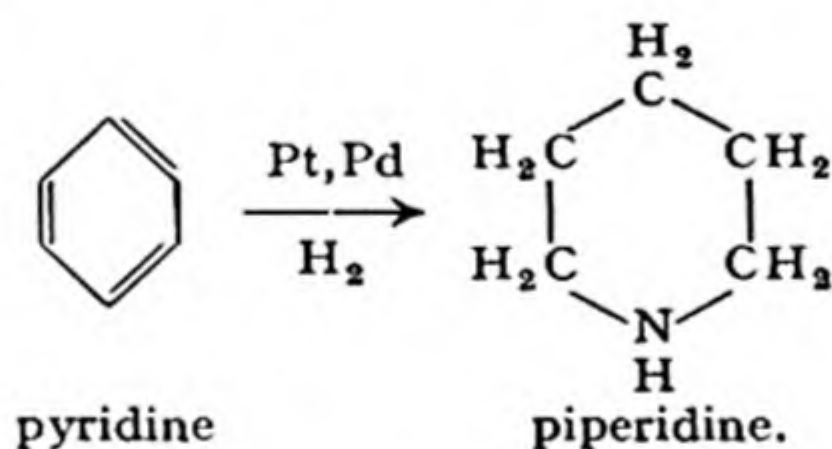


I has the properties of a quaternary ammonium salt and is soluble in water. When I is treated with sodium carbonate, the corresponding ammonium base (II) is produced as a red, crystalline compound from which I may be regenerated by the action of hydrogen chloride in glacial acetic acid solution. However, when a solution of the ammonium base in dilute hydrochloric acid is warmed, 2,4-dinitroaniline separates. The solution contains glutaconic dialdehyde, this can be detected by the addition of aniline, when the red dianil of glutaconic aldehyde is precipitated. In this reaction the pyridine ring is opened by hydrolytic fission:



Hydrogenation products of pyridine. By catalytic hydrogenation with platinum or palladium at slightly increased temperatures, pyridine is converted into piperidine (for the converse reaction see p. 555). This reaction is similar to the formation of cyclohexane from benzene.

With pyridine and its homologues, the reduction may also be carried out with sodium and boiling alcohol (LADENBURG):

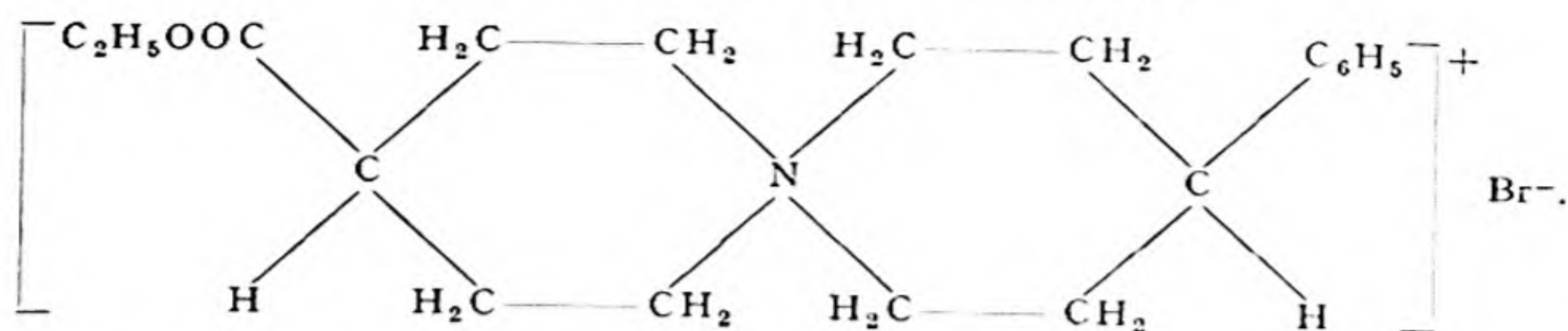


When pyridine is heated with hydroiodic acid at 300°, ring-fission as well as reduction occurs with the production of *n*-pentane and ammonia.

Piperidine or *hexahydropyridine* C₅H₁₁N, is a colourless liquid with an amine-like odour, which is miscible in all proportions with water. The aqueous solution colours litmus blue. Piperidine boils at 106.4°, melts at -10.5° and has $d_4^{20} = 0.861$. It is a secondary base forming a nitroso-compound and well defined crystalline salts and double-salts.

Piperidine reduces ammoniacal silver solution with the deposition of silver. The alkaloid piperine (354) is a derivative of piperidine.

4-Phenyl-4'-carbethoxy-spiro-bispiperidinium bromide is a remarkable compound from a stereochemical point of view:



Its nitrogen atom forms part of two piperidine rings and is attached with four homopolar bonds to carbon atoms; hence the bromide is a quaternary ammonium salt. If it is assumed, that the bonds around the nitrogen atom are distributed tetrahedrally, the two piperidine rings must lie in planes which are perpendicular to one other. The space model shows a similarity to that of a substituted allene (see 92); it is asymmetric so that the cation must occur in mirror-image forms. Actually this compound has been resolved into optically active forms by MILLS.

The structure of the bispiperidinium derivative is similar to that of *spirocyclic carbon rings* (292).

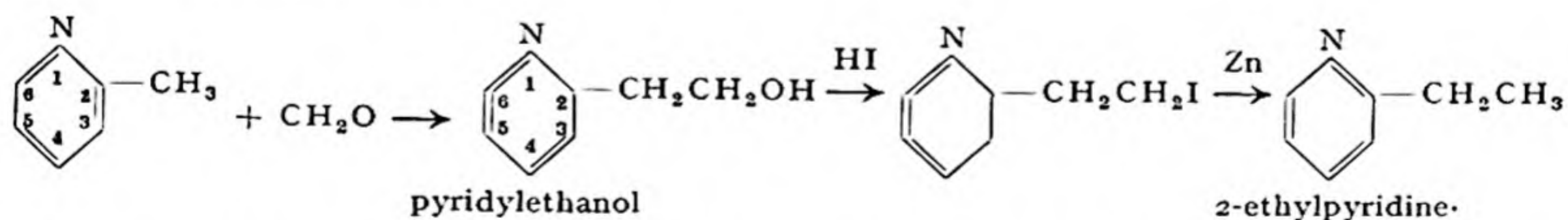
Homologues of pyridine

333. The *picolines* C_6H_7N or *methylpyridines*, the *lutidines* C_7H_9N or *dimethylpyridines*, the *collidines* $C_8H_{11}N$ or *trimethylpyridines* and the *parvolines* $C_9H_{13}N$ or *tetramethylpyridines* are amongst the homologues of pyridine.

These compounds can be obtained from coal-tar in which they occur to the extent of 0.05–0.1 % in all. Some occur also in distillates from Californian petroleum; dimethylpyridines and methylethylpyridines also occur along with other compounds in DIPPEL's bone oil (314).

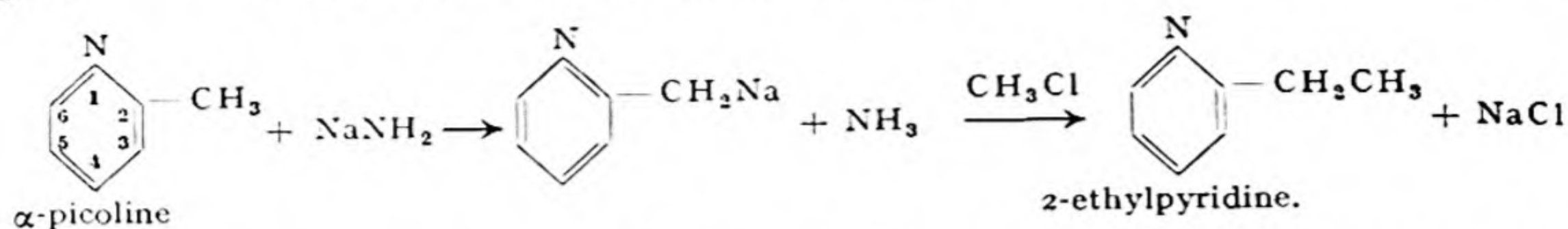
Since the boiling points of isomeric homologues lie close together, some of these compounds are extremely difficult to obtain pure.

Methylpyridines in which the methyl group is situated in positions 2 or 4, can undergo condensation reactions with aldehydes; methyl groups in the 3-position cannot do this:



Thus α -picoline condenses with formaldehyde to give pyridylethanol and when this alcohol is treated with hydriodic acid and then with zinc dust, *2-ethylpyridine* is produced.

Homologues with longer side-chains can be obtained from those with shorter chains by the method of TSCHITSCHIBABIN. For this purpose, soda-mide is added to 2- or 4-methylpyridine and then an alkyl halide when the following reaction takes place:

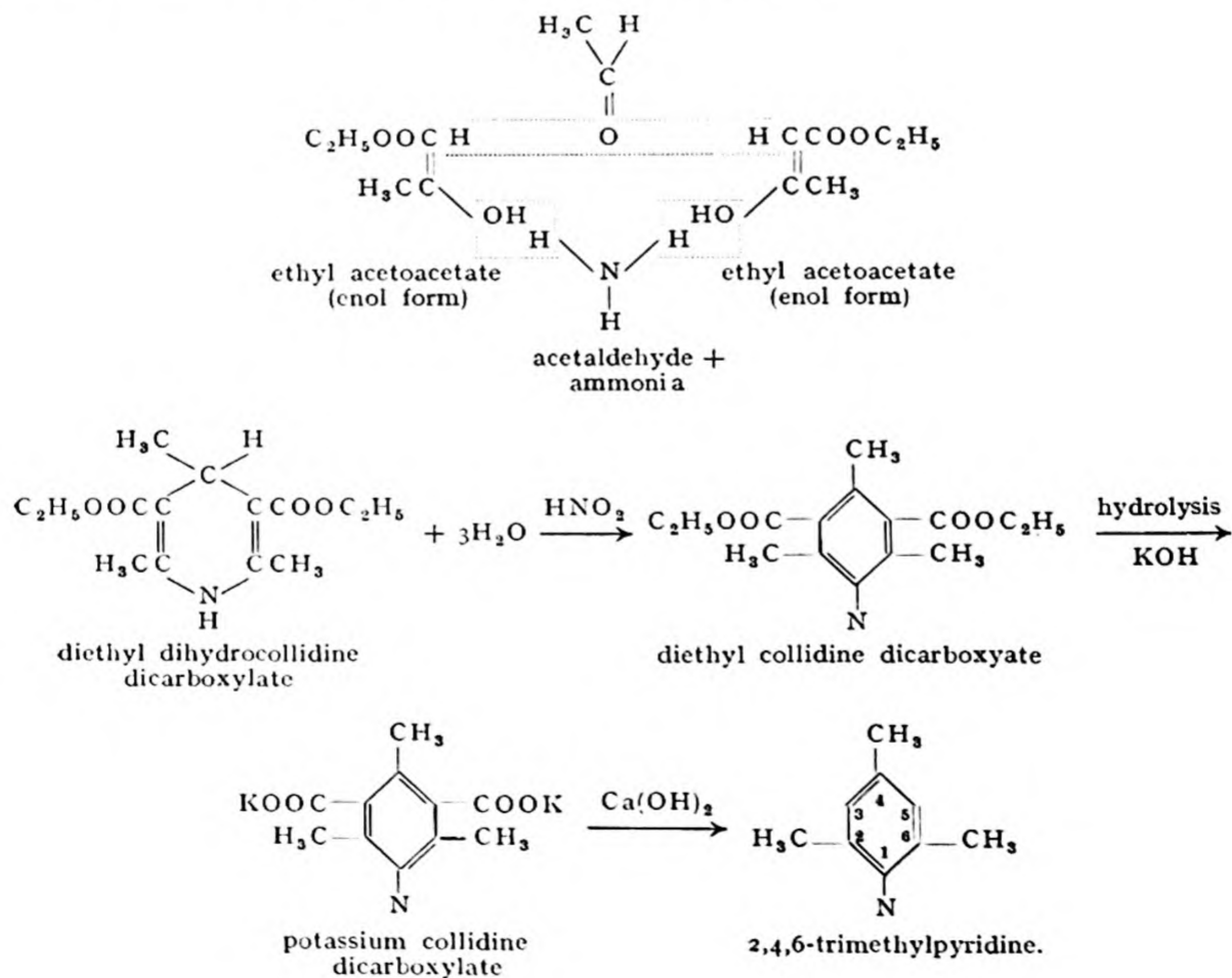


Mono-methylpyridines or *picolines*, 2- or α -picoline occurs chiefly in coal-tar; it is a colourless liquid boiling at 129° . 3- or β -picoline, is miscible with water in all proportions like 2-picoline and boils at 143° . 4- or γ -picoline boils at 145° and is the least accessible of the isomers.

On oxidation with potassium permanganate the picolines are converted into pyridine mono-carboxylic acids, viz. *picolinic acid*, *nicotinic acid* and *iso-nicotinic acid* respectively. (See page 565).

Dimethylpyridines or *lutidines* and *trimethylpyridines* or *collidines* can be prepared by the HANTZSCH synthesis.

For the preparation of collidine, ethyl acetoacetate (148) is warmed with aldehyde ammonia (60) to give a condensation product, *diethyl dihydrocollidine dicarboxylate*; this ester loses two atoms of hydrogen when heated with nitrous acid, giving *diethyl collidine dicarboxylate*:

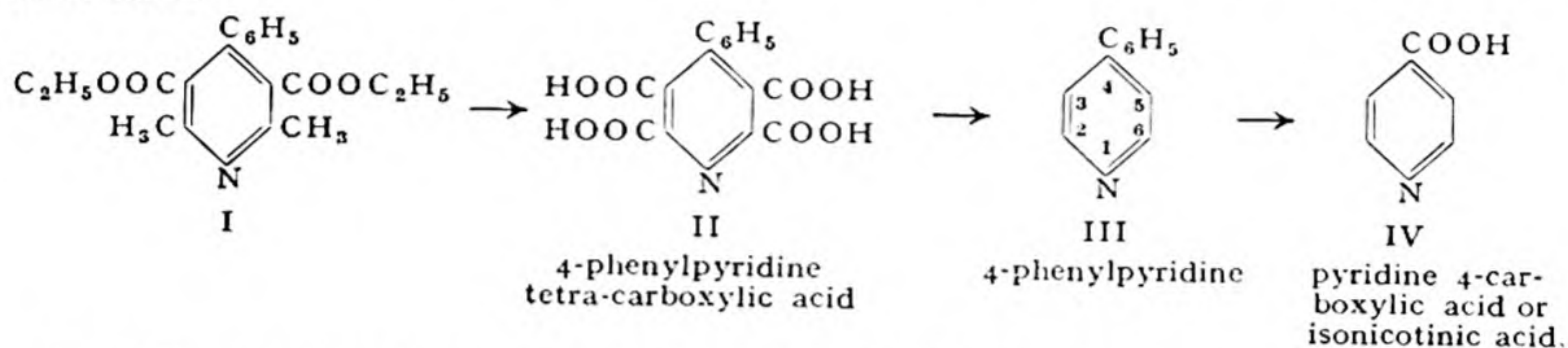


After hydrolysing the ester with caustic potash, the potassium salt of collidine dicarboxylic acid is produced, which may be converted into symmetrical collidine with the elimination of the carboxyl groups as carbon dioxide, by heating with lime.

α -Lutidine or 2,6-dimethylpyridine is prepared in a similar way from ethyl acetoacetate, formaldehyde and ammonia.

The fact that the carbon atom in the aldehydic carbonyl group forms carbon atom 4 in the pyridine ring in this synthesis, is proved as follows.

By the interaction of benzaldehyde, ammonia and ethyl acetoacetate there is produced compound I, from which compound II is formed by hydrolysis and oxidation with potassium permanganate and this compound is converted into III by distillation with lime:



A small quantity of a pyridine carboxylic acid (IV) can be obtained from III by long boiling with potassium permanganate solution. Hence the phenyl nucleus is disrupted rather more readily than the pyridine nucleus. This pyridine carboxylic acid is identical with isonicotinic acid, the structure of which has been definitely proved (336).

Of the lutidines, 2,4- and 2,6-dimethylpyridine have been prepared synthetically; they boil respectively at 158° and 145° .

2-Methyl-5-ethylpyridine or aldehydecollidine is the chief component of the pyridine bases produced by heating acetaldehyde ammonia (1 mol.) with paraldehyde (3 mols.) to 220° . It boils at 174° .

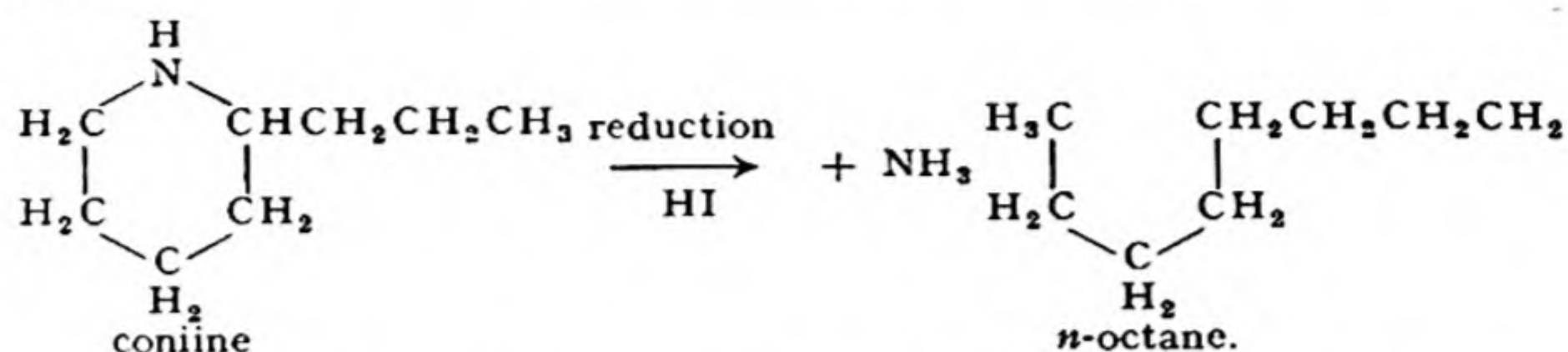
Finally 4-methyl-3-ethylpyridine or β -collidine and 2-propylpyridine or conyrine should be mentioned.

Orientation of pyridine derivatives

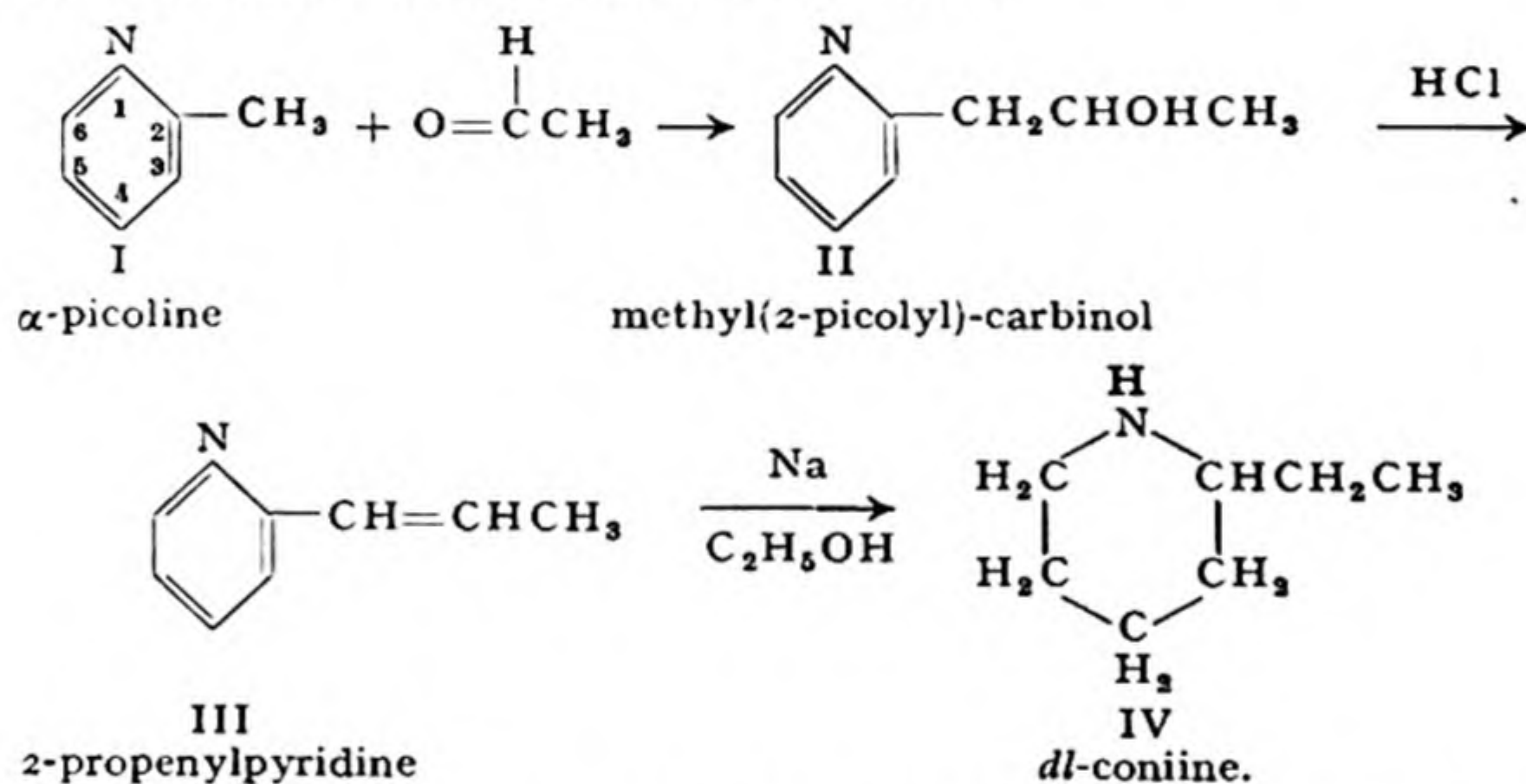
334. The picoline boiling at 129° is 2-methylpyridine, as is apparent from the relationship between this compound and coniine an alkaloid (352) occurring in hemlock. When coniine $\text{C}_8\text{H}_{17}\text{N}$ is distilled over zinc dust or is heated with silver acetate, a base, conyrine $\text{C}_8\text{H}_{11}\text{N}$, containing six less atoms of hydrogen, is produced. On oxidation with potassium permanganate, the latter compound gives picolinic acid. From this it follows that conyrine contains a pyridine nucleus and a propyl group as a side-chain: $\text{C}_5\text{H}_4\text{NC}_3\text{H}_7$ (HOFMANN). Thus it is probable that coniine is a propylpiperidine.

Ammonium iodide and *n*-octane are produced when coniine is heated to 300° with hydriodic acid. The side chain must be a normal propyl group

therefore and must be situated in the 2-position in the piperidine ring, since only in this particular case can the molecule possess a normal chain of eight carbon atoms:



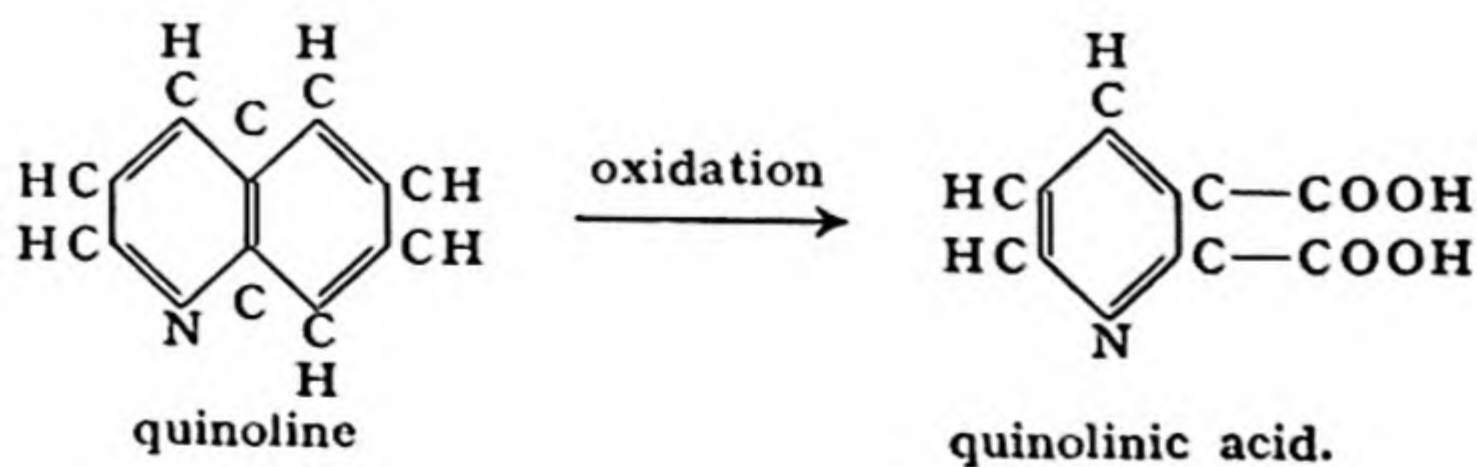
The structure of coniine has been confirmed by its synthesis by LADENBURG (1886). By heating α -picoline (I) with acetaldehyde he obtained *methyl-(2-picolyl)carbinol* (II). By heating with hydrochloric acid, water was eliminated from this compound with the production of *2-propenylpyridine* (III). This compound was reduced with sodium and alcohol when *dl*-coniine (IV) was produced. *l*-Coniine was obtained by resolving the tartrate and was found to be identical with natural coniine:



As has already been proved, the side-chain in coniine is in the 2-position; therefore, α -picoline must be 2-methylpyridine and picolinic acid obtained by oxidising α -picoline must be pyridine 2-carboxylic acid.

The structure of the two remaining pyridine carboxylic acids is given as follows:

By oxidising quinoline, the structure of which is proved in 337, a pyridine dicarboxylic acid, *quinolinic acid*, is produced, which must therefore have the following structure:



On heating quinolinic acid, a molecule of carbon dioxide is easily eliminated with the production of a pyridine monocarboxylic which is not identical with picolinic acid. Hence this must be pyridine 3-carboxylic acid and is called nicotinic acid because it can be obtained by the oxidation of nicotine (355). The third pyridine monocarboxylic acid must then be pyridine-4-carboxylic acid; this is isonicotinic acid.

The pyridine monocarboxylic acids can be converted into aminopyridines by the HOFMANN reaction (78); in this way the structure of the aminopyridines is established.

Substitution products of pyridine

335. Various substituents can be introduced into the pyridine nucleus in the same way as into the benzene nucleus; as a rule, however, substitution in the pyridine nucleus takes place with much greater difficulty.

Pyridine-sulphonic acids. 3-Pyridinesulphonic acid is produced by heating pyridine sulphate with fuming sulphuric acid at 300°.

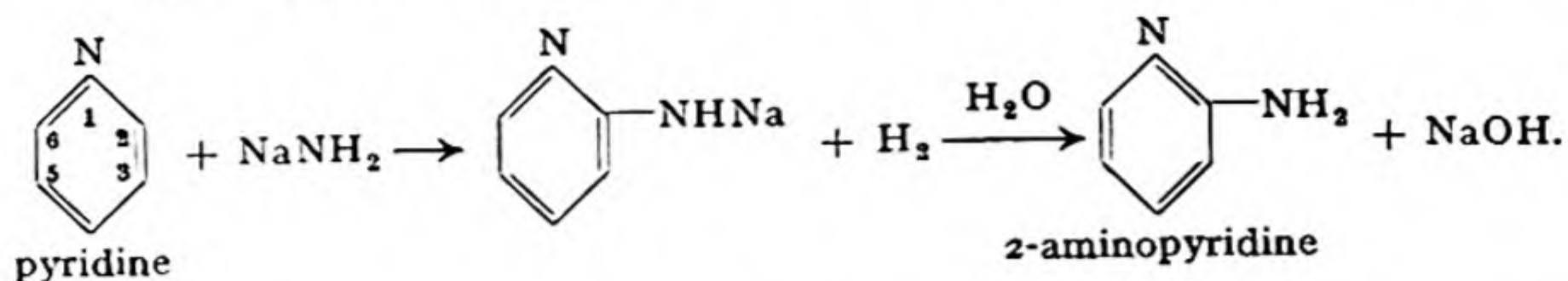
When mercuric sulphate is added to the mixture, the reaction takes place at a lower temperature and a mixture of 2- and 3-pyridinesulphonic acids is produced (WIBAUT & VAN GASTEL).

Nitropyridines (C_5H_4N)NO₂. 3-Nitropyridine is produced when pyridine is heated with oleum and potassium nitrate at 330°. When the reaction is carried out at 450°, 2-nitropyridine is produced (DEN HERTOOG and OVERHOFF). The yields are very small however.

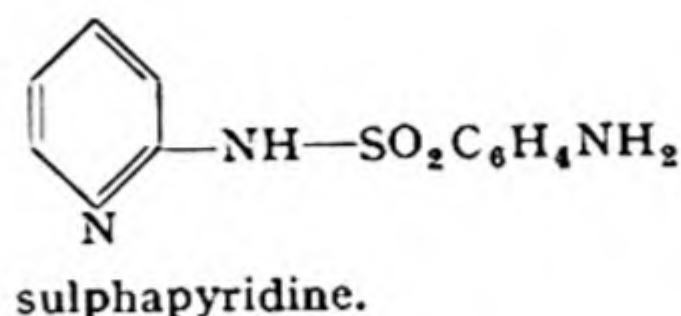
Halogenopyridines (C_5H_4N)Hal. In the bromination of pyridine, temperature has a great effect on the position taken up by the entering bromine atoms. By the action of bromine on pyridine in the vapour-phase at 300°, a mixture of 3-bromopyridine and 3,5-dibromopyridine is produced; when the reaction is carried out at 500°, 2-bromopyridine is formed along with 2,6-dibromopyridine (WIBAUT and DEN HERTOOG); in the chlorination of pyridine vapour again the chlorine atom may enter position 2 or positions 3 and 5 depending on the temperature (compare similar phenomena in the bromination of halogenobenzenes and naphthalene 272, 281).

Halogen atoms substituted in positions 2 or 4 in the pyridine nucleus may be replaced by other groups of atoms; on the other hand, halogen atoms substituted in the 3-position are much more difficult to replace. They are comparable with halogen atoms attached to the benzene nucleus.

Aminopyridines (C_5H_4N)NH₂. 2-Aminopyridine, melting at 57°, is obtained by heating 2-chloro- or 2-bromopyridine with ammonia. An important method of preparing 2-aminopyridine is by heating pyridine with sodamide in toluene solution (TSCHITSCHIBABIN and SEIDE):



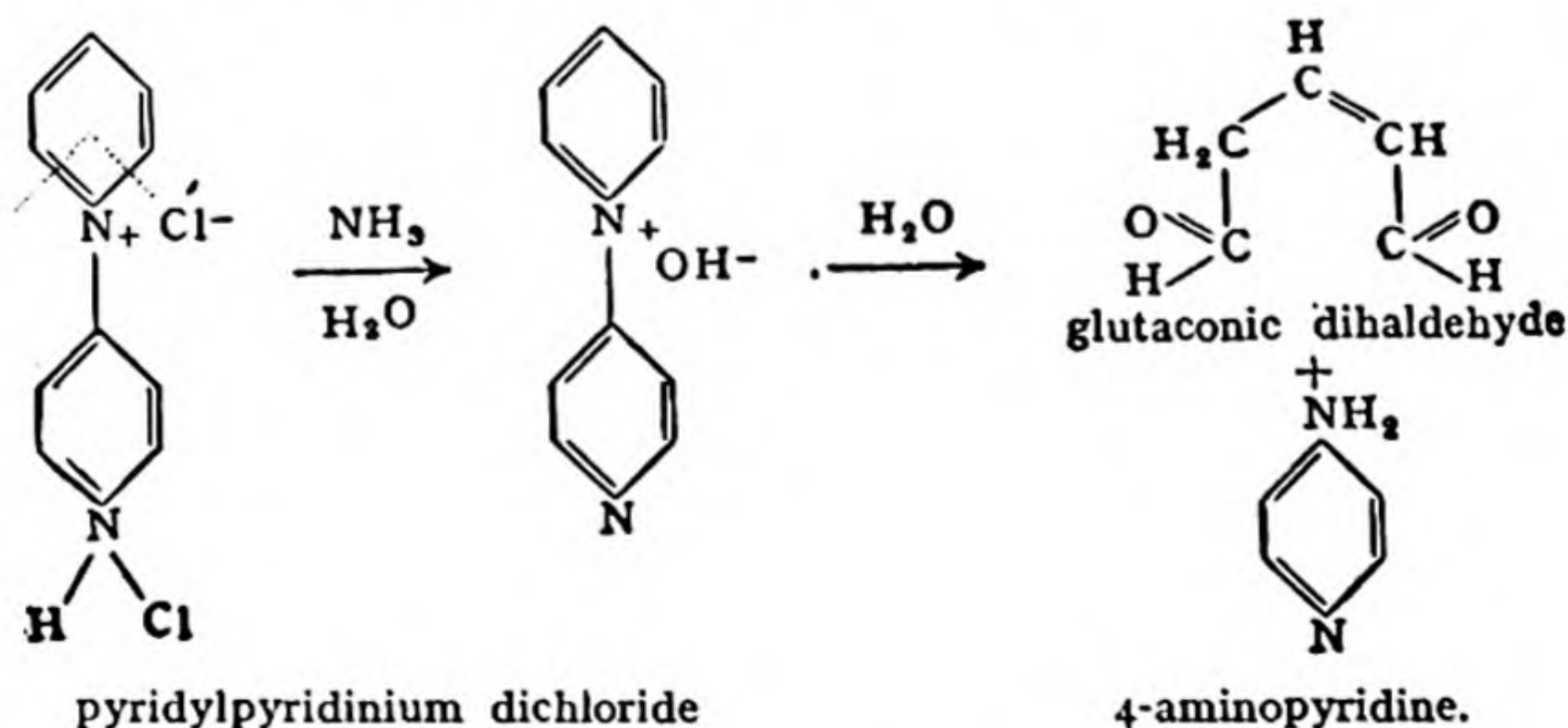
2-Aminopyridine is of importance for the preparation of *sulphapyridine*, used in medicine against infectious diseases caused by streptococci. It has a similar action to Prontosil (254):



3-Aminopyridine is produced by reducing 3-nitro-pyridine. It can however be prepared by heating 3-bromopyridine to 200° with aqueous ammonia containing copper sulphate as a catalyst. 3-Aminopyridine melts at 64° ; it reacts with nitrous acid in hydrochloric acid with the formation of a diazonium salt which has similar properties to the diazonium salts from aromatic amines (236). Under these conditions no diazonium salts are produced from 2- and 4-aminopyridines, which are directly converted into the corresponding hydroxypyridines.

4-Aminopyridine, melting at 158° , can be obtained by the reaction of KÖNIGS and GREINER.

Pyridylpyridinium dichloride (I) is produced by the action of thionyl chloride SOCl_2 on pyridine at ordinary temperatures. In this reaction the thionyl chloride acts as a dehydrogenating agent. By hydrolytic fission, which is best carried out by heating with concentrated ammonia at 150° , I is converted into 4-aminopyridine and glutaconic dialdehyde (cf. p. 558):



Hydroxypyridines $\text{C}_5\text{H}_4\text{N}(\text{OH})$. 2- and 4-Hydroxypyridines can be prepared from the corresponding aminopyridines. 3-Hydroxypyridine can be obtained by fusing pyridine-3-sulphonic acid with caustic potash. The hydroxypyrid-

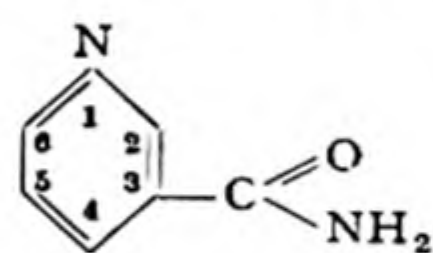
ines are readily soluble in water and they give metal compounds with alkalis, which are similar to the phenates (229).

The *pyridine monocarboxylic acids* $(C_5H_4N)COOH$ are obtained by oxidising the appropriate picolines. *Picolinic acid* or *pyridine 2-carboxylic acid* melts at 139° , is easily soluble in water and alcohol but is sparingly soluble in ether and chloroform. *Nicotinic acid* or *pyridine 3-carboxylic acid* melts at 229° and is readily soluble in hot water and hot alcohol but difficultly soluble in ether. *Isonicotinic acid* or *pyridine 4-carboxylic acid* melts at 317° , is sparingly soluble in cold but readily soluble in warm water and practically insoluble in boiling alcohol.

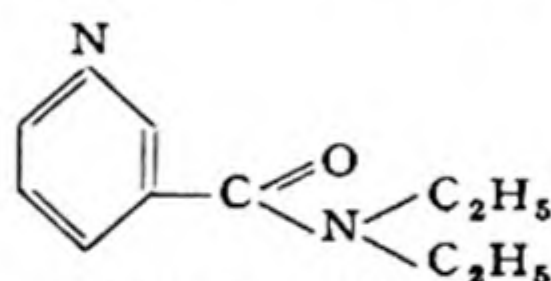
These acids are amphoteric in character, *i.e.* they form salts with acids on the nuclear nitrogen atom but react also with bases to give salts of carboxylic acids.

Nicotinic acid and *nicotinamide* $C_5H_4NCONH_2$ are of importance in biochemistry (306, 351).

Nicotindietiethylamide is known under the name of *coramine* and is used in medicine as a substitute for camphor preparations; it is soluble in water:



nicotinamide



nicotindietiethylamide.

Pyridine dicarboxylic acids $C_5H_3N(COOH)_2$. The dicarboxylic acids are frequently met with amongst the oxidation products of alkaloids and quinoline derivatives and they are of importance in determining the structure of these compounds.

Quinolinic acid or *pyridine 2,3-dicarboxylic acid* melts at $175-190^\circ$ and is prepared from quinoline (337).

Cinchomeric acid or *pyridine 3,4-dicarboxylic acid* melts at 258° and is prepared from either quinine or cinchonine (358). *Lutidinic acid* or *pyridine 2,4-dicarboxylic acid* melts at 250° and is prepared from 2,4-lutidine.

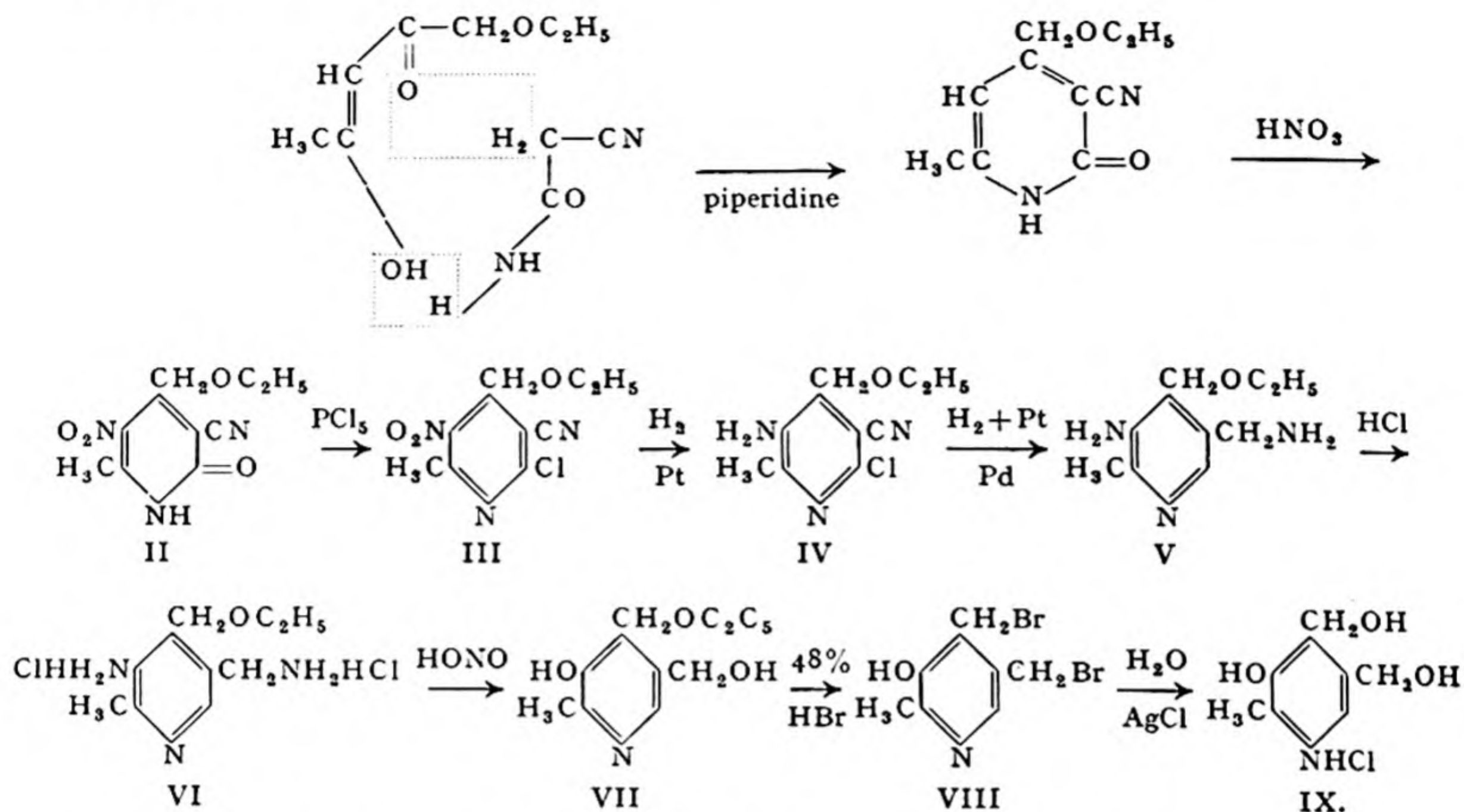
Pyridine tricarboxylic acids $C_5H_2N(COOH)_3$. *Berberonic acid* or *pyridine 2,4,5-tricarboxylic acid*, melting at 243° , is produced from the alkaloid berberine. *Carbocinchomeric acid* or *pyridine 2,3,4-tricarboxylic acid* melts at 250° and is produced from quinine and cinchonine.

All pyridine carboxylic acids, that have a $COOH$ -group in an α -position, give a yellow colour with a solution of $FeSO_4$.

Vitamin-B₆, pyridoxin or adermin

336. *Pyridoxin* is a biochemically important derivative of pyridine, which protects the body against dermatitis and promotes growth. The structure of this vitamin was elucidated by KUHN and definitely proved by a synthesis carried out by HARRIS and his collaborators (1939).

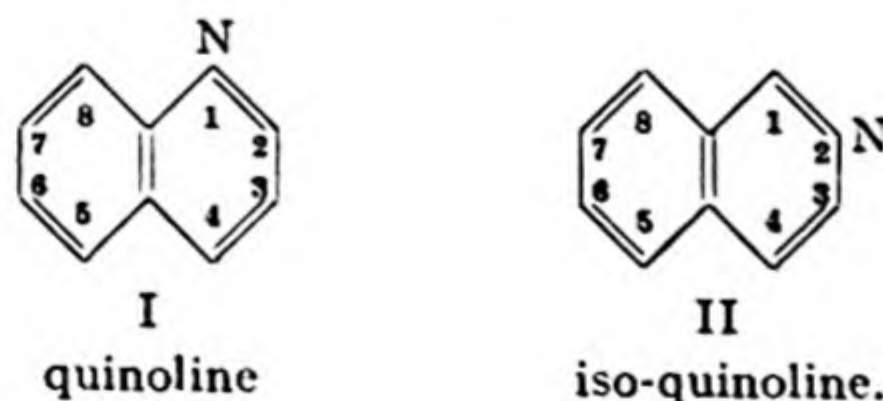
The starting materials are ethoxyacetylacetone and cyanacetamide from which 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (I) is produced on the addition of piperidine (332):



By heating I with fuming nitric acid it is converted into a nitro-compound (II), which forms a chloronitro-compound (III) on treatment with phosphorus pentachloride. After catalytic reduction in a two stage process, compound V is produced and the hydrochloride of this compound (VI) is converted into the hydroxy compound (VII) by treatment with nitrous acid. Treatment with 48 % hydrobromic acid produces VIII, which affords the hydrochloride of pyridoxine (IX) by the action of silver chloride and water; the free base is identical with naturally occurring vitamin-B₆.

Quinolines

337. The pyridine nucleus can be condensed in *ortho*-positions with a benzene nucleus in two different ways, viz:

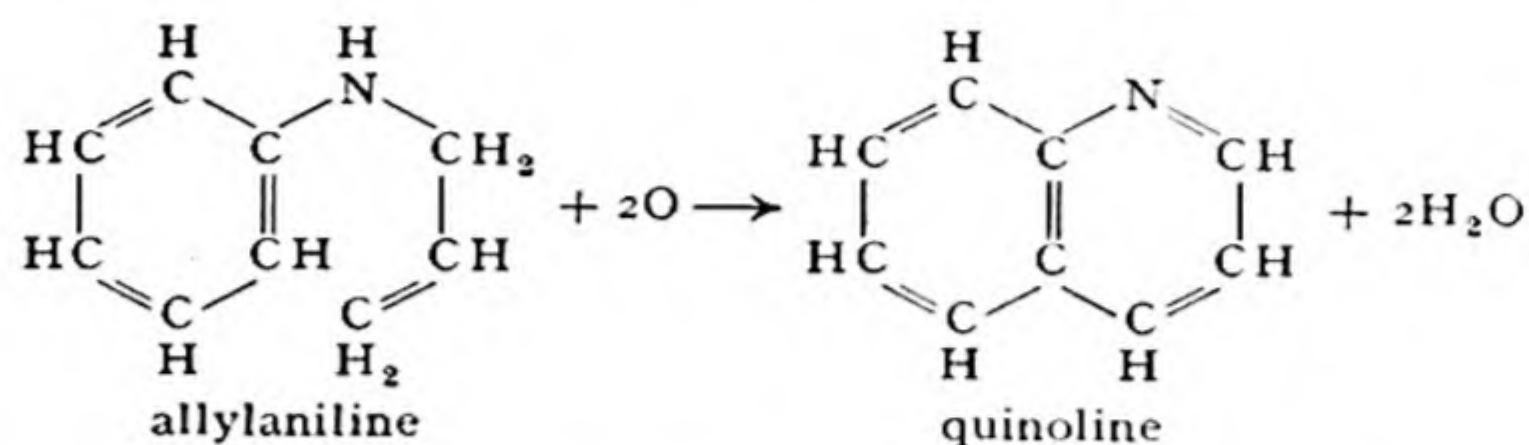


A large number of derivatives can be derived from these quinolines.

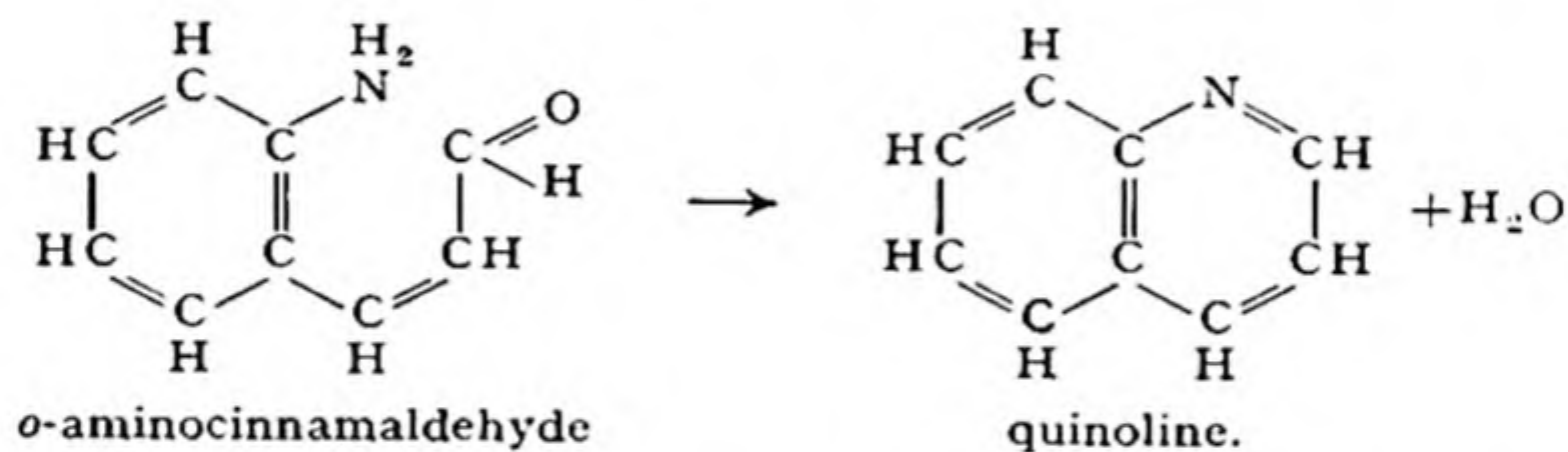
Quinoline $\text{C}_8\text{H}_7\text{N}$ was obtained in an impure state in 1842 by GERHARDT by distilling cinchonine (359) with caustic potash solution. The name quinoline is derived from this method of formation from the cinchona alkaloids.

The compound also occurs in very small quantities, mixed with its homologues, in coal-tar. Quinoline is a weak tertiary base insoluble in water. It has a sharp odour, forms salts with acids, boils at 237° and melts at -15.6° .

Structure of quinoline. This is proved 1, by KÖNIG's synthesis, in which allylaniline vapour is passed over red-hot lead oxide:



2, by reduction of *o*-nitrocinnamaldehyde when the initial product is *o*-aminocinnamaldehyde, which is converted into quinoline with the loss



of a molecule of water. From these syntheses it follows that quinoline is an *ortho*-substituted benzene. The structure of the ring containing nitrogen follows from the oxidation of quinoline to the dibasic quinolinic acid (335) from which pyridine is produced by distillation with lime.

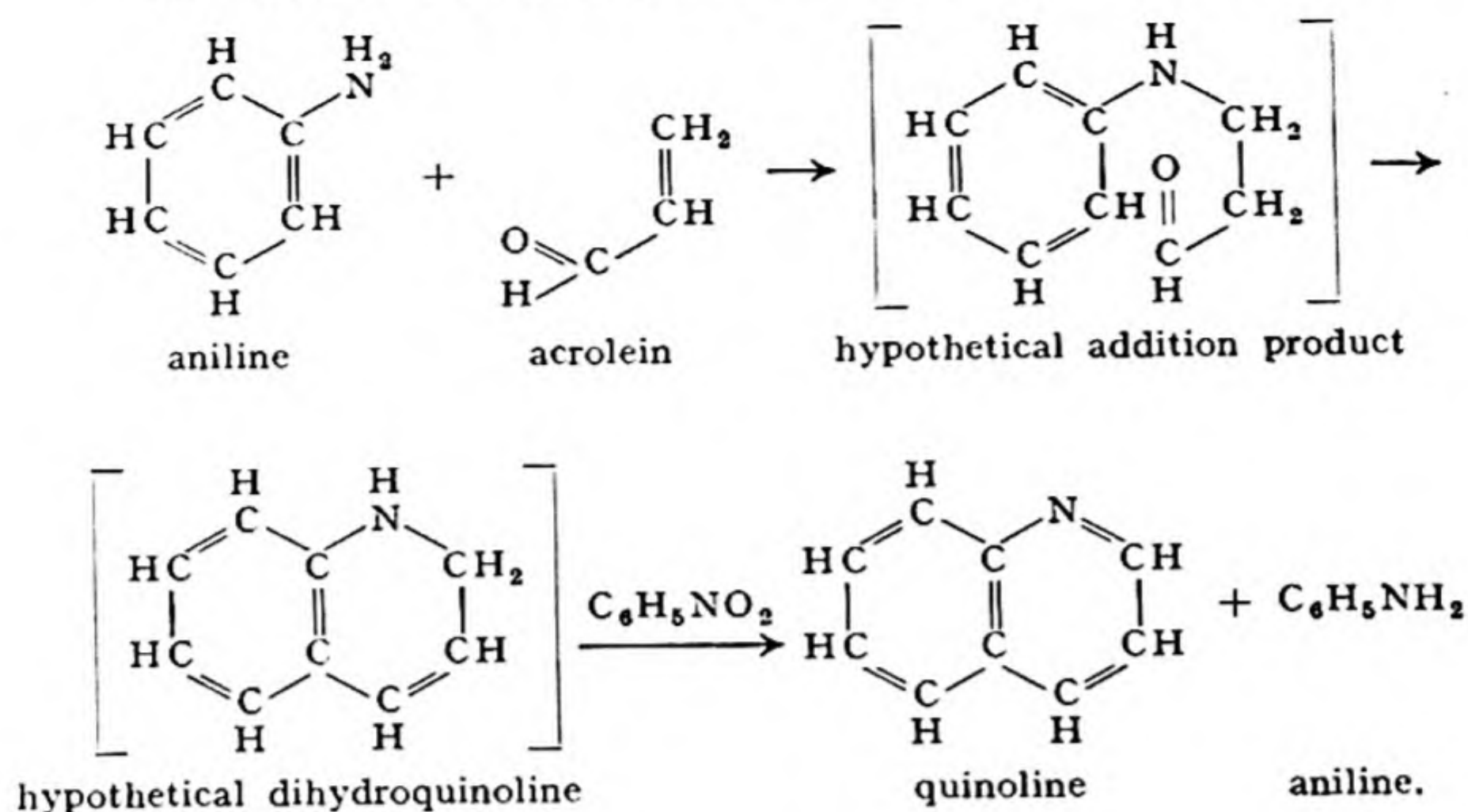
From this it follows that *quinoline contains a pyridine nucleus and a benzene nucleus having two carbon atoms in ortho-positions in common. It may be regarded as being derived from naphthalene by replacing one of the CH-groups in the 1-position by N.*

Quinoline and its homologues can be prepared in various ways.

1st By the SKRAUP synthesis.

A primary aromatic amine with a free *ortho*-position is heated with an aromatic nitro-compound corresponding with the amine, glycerol and concentrated sulphuric acid. Acrolein is produced by the action of concentrated sulphuric acid on glycerol and it is assumed that this substance forms an addition product with the aromatic amine, which is converted into *dihydroquinoline* with the loss of water. The latter is then oxidised to quinoline by the aromatic nitro-compound, which is, in its turn, reduced to the corresponding amine.

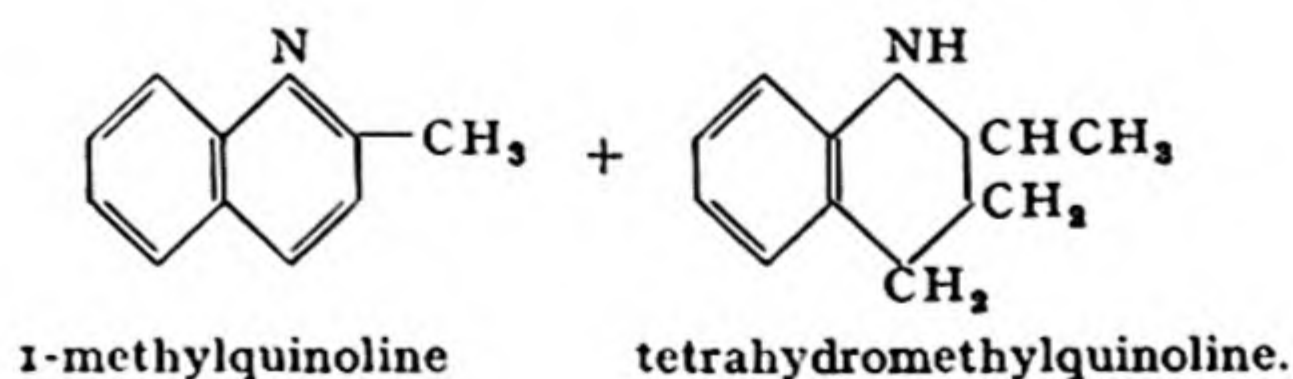
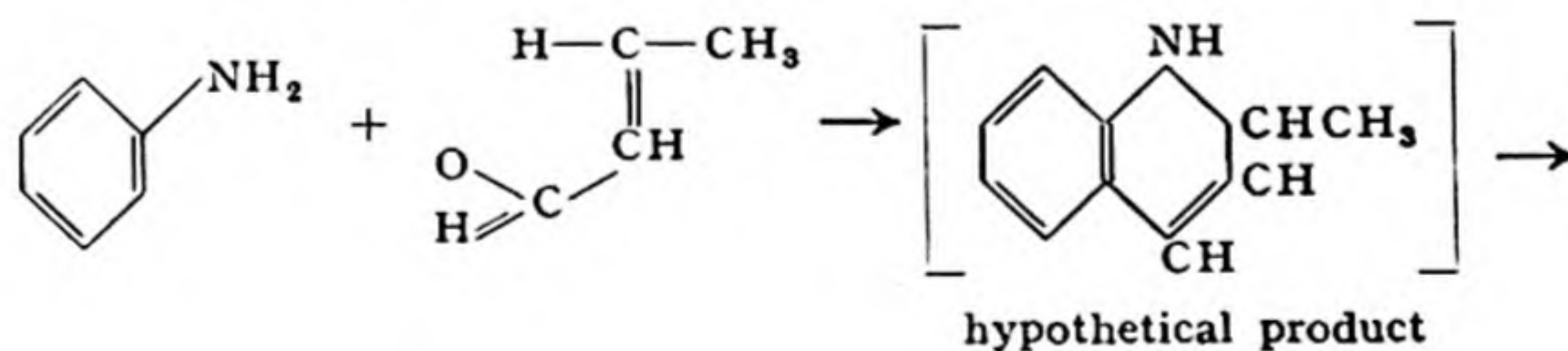
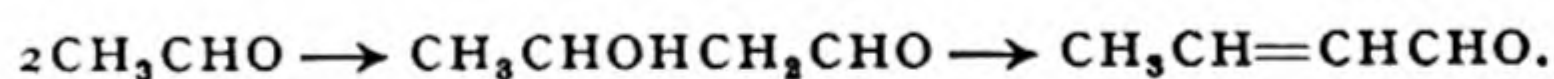
In this way, quinoline is prepared from aniline, glycerol and nitrobenzene:



Other mild oxidising agents such as arsenic oxide may be used instead of nitrobenzene. The synthesis may be carried out also with substituted anilines.

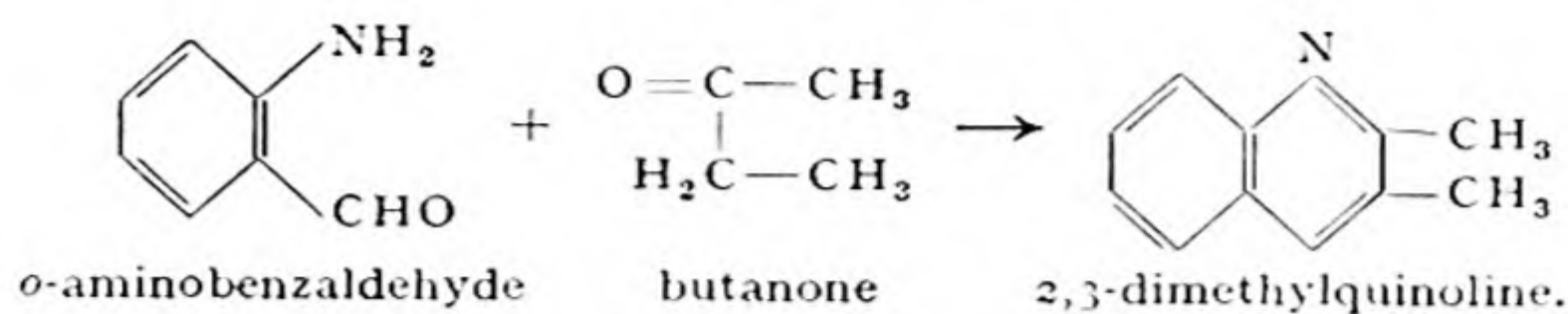
2nd By the DÖBNER-MILLER synthesis.

This synthesis can be used only for homologues of quinoline. A primary aromatic amine is heated with two molecular proportions of an aliphatic aldehyde and concentrated sulphuric acid. The two molecules of aldehyde probably combine to form an aldol, which loses a molecule of water and is converted into the 1,2-unsaturated aldehyde. The latter then condenses with the aromatic amine giving a derivative of dihydroquinoline, which is converted finally into a mixture of the corresponding quinoline and tetrahydroquinoline, thus:



3rd By the FRIEDLÄNDER synthesis.

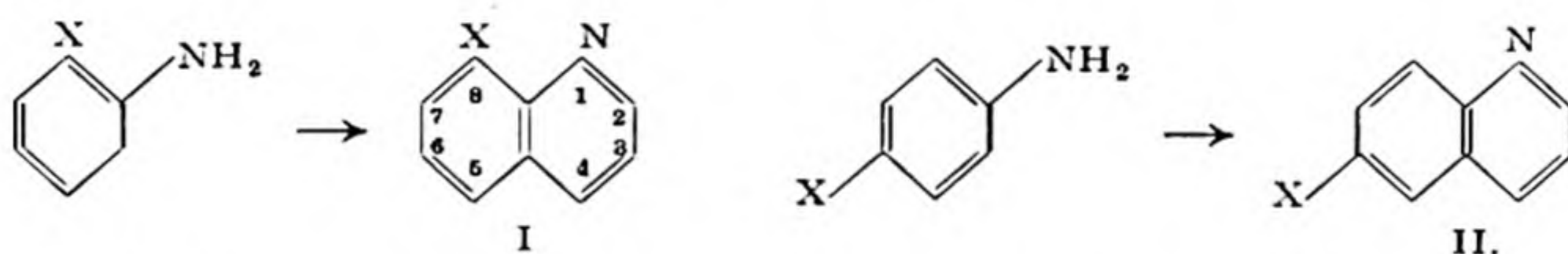
o-Aminobenzaldehyde is condensed in an alkaline medium with an aldehyde or a ketone having a methylene group next to the carbonyl group:



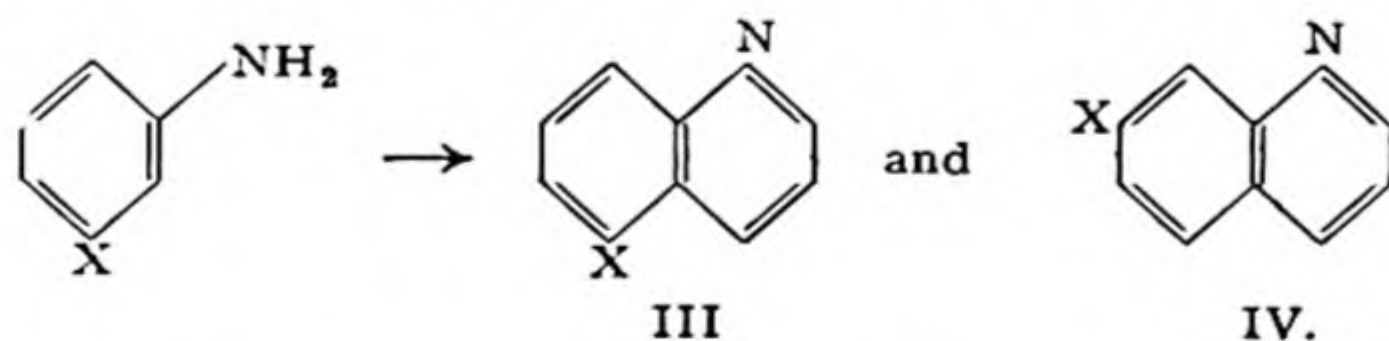
The number of isomeric substitution products of quinoline is very large. Seven monosubstitution products are possible because none of the seven atoms of hydrogen are situated in equivalent positions with respect to the nitrogen atom. The number of disubstitution products carrying like substituents is 21.

Orientation of substituents. This can be done by three methods, viz. by relative orientation (217), by oxidation and by the SKRAUP synthesis. In the second method, the pyridine ring remains intact, so that it may be determined which substituents are present in the benzene nucleus and which in the pyridine nucleus. When a substituted aniline is used in the SKRAUP synthesis, the substituents in the resultant quinoline derivative are present in the benzene nucleus; incidentally, in the case of *ortho*- and *para*-substituted anilines the position of the substituent in the resultant quinoline, is definitely established.

Only an 8-substituted quinoline (I) can arise from an *ortho*-substituted aniline:



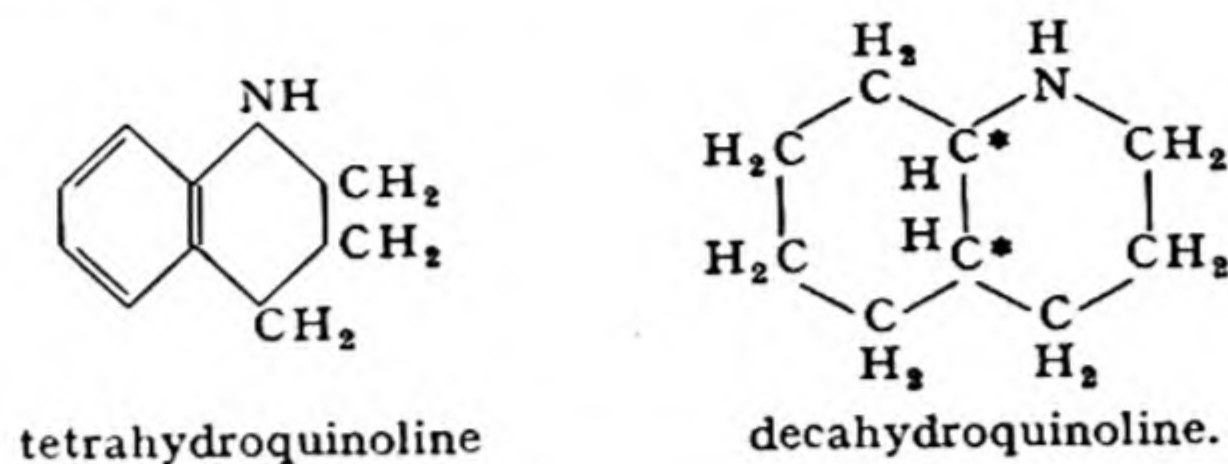
Only a 6-substituted quinoline (II) can result from a *para*-substituted aniline. But two quinolines (III) and (IV) can be produced from a *meta*-substituted aniline, so that all four possible quinoline derivatives with substituents in the benzene ring can be obtained by the SKRAUP synthesis:



Hydrogenation products of quinoline. On hydrogenation, hydrogen is first of all taken up by the pyridine ring independently of how the reduction is carried out, so that *tetrahydroquinoline* is produced. This is a powerful secondary base boiling at 248°.

On further reduction with a nickel or palladium catalyst the benzene ring also is hydrogenated and *decahydroquinoline* is produced. This compound has all the characteristics of a secondary aliphatic amine; it melts at 48°

and boils at 204° at 714 mms. Two unlike asymmetric carbon atoms occur in the molecule; from the possible isomers two mirror image forms have been obtained with $[\alpha]_D = \pm 4.5^{\circ}$:



Homologues of quinoline. α - or 2-Methylquinoline or quinaldine is produced from aniline and acetaldehyde by the DÖBNER-MILLER synthesis. It boils at $246-248^{\circ}/755$ mms.

The hydrogen atoms in the methyl group in the 2-position are reactive like those in the 2-methylpyridines; quinaldine can undergo condensation reactions with aldehydes.

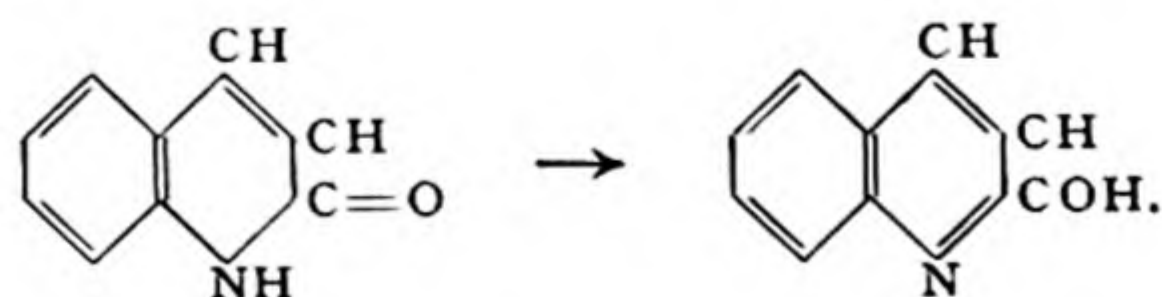
Quinoline Yellow is a dyestuff derived from quinaldine; it is produced by condensing phthalic anhydride with quinaldine in presence of zinc chloride, sulphonating the product and converting it into the sodium salt.

γ - or 4-Methylquinoline or lepidine was first observed amongst the decomposition products from quinine alkaloids. It boils at $258-260^{\circ}/742$ mms. The hydrogen atoms in the methyl group are reactive.

A number of methyl derivatives of quinoline like 2,3-dimethyl-, 2,4-dimethyl-, 2,8-dimethyl-, 2,4,8-trimethyl-quinoline and others, have been isolated from distillates from Californian petroleum.

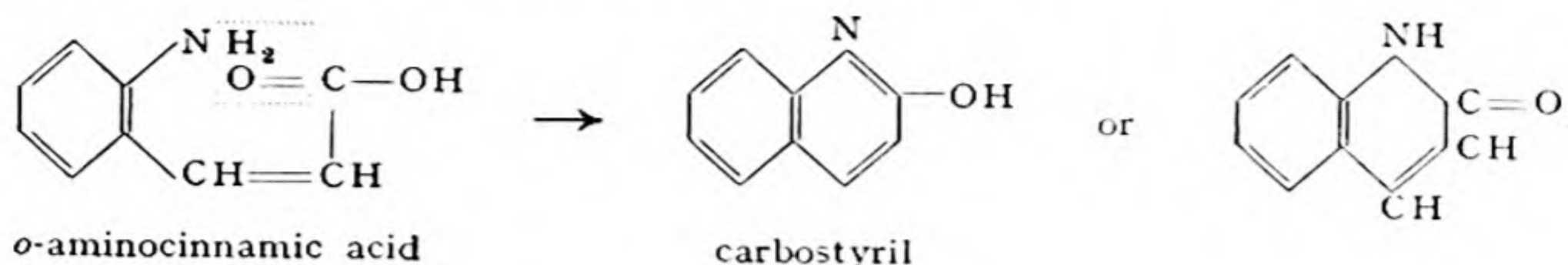
Substituted quinolines

338. *Hydroxyquinolines* or *quinolones*. Of these compounds, 2- or α -hydroxy-quinoline or *carbostyryl* has been studied very exhaustively because it occurs in tautomeric forms:

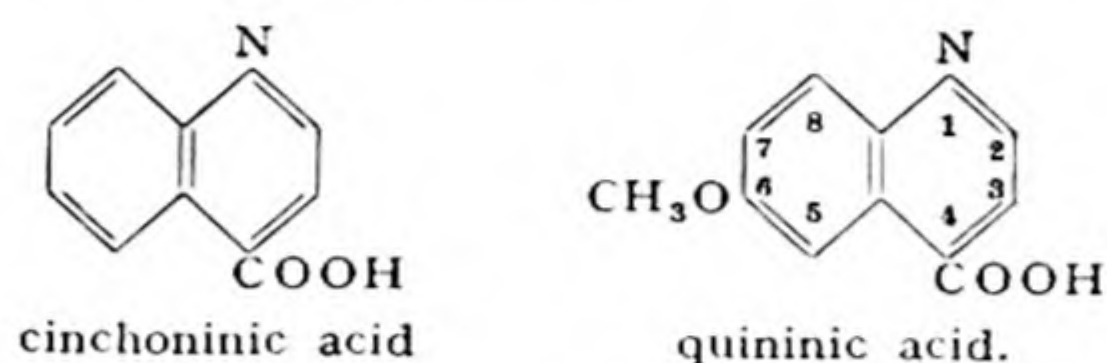


It melts at 200° and has the properties of a phenol, namely, it is soluble in caustic alkali solution and is reprecipitated from the alkaline solution by carbon dioxide.

Carbostyryl was first obtained by reducing *cis*-*o*-nitrocinnamic acid; the initial product is aminocinnamic acid from which a molecule of water is eliminated (CHIOZZA 1852). The structure follows from this synthesis:



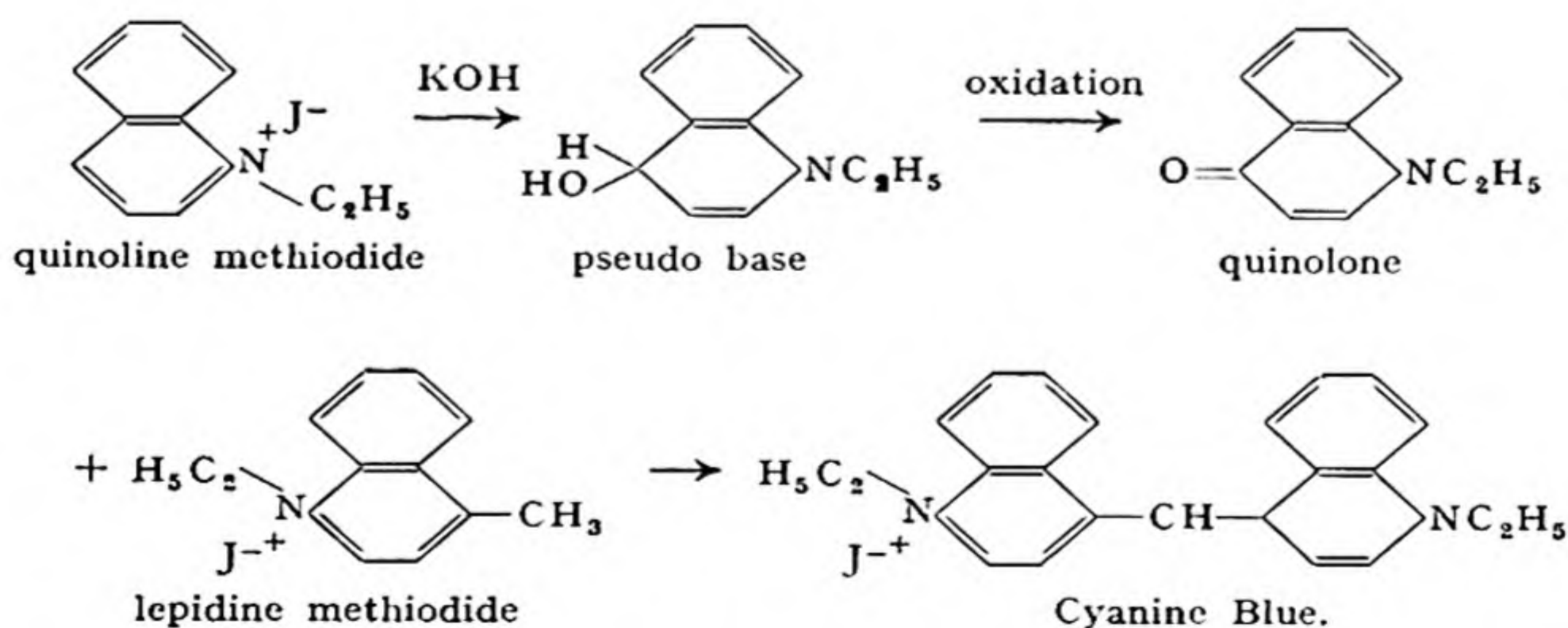
Quinoline carboxylic acids. *Cinchoninic acid* or *quinoline 4-carboxylic acid* and its 6-methoxy-derivative, *quininic acid*, are of importance on account of their relationship with the alkaloids cinchonine and quinine (358), from which they are produced by oxidation:



On distillation with lime, these acids are converted respectively into quinoline and 6-methoxyquinoline. The position of the carboxyl group in cinchoninic acid is established by oxidative degradation to pyridine 2,3,4-tricarboxylic acid.

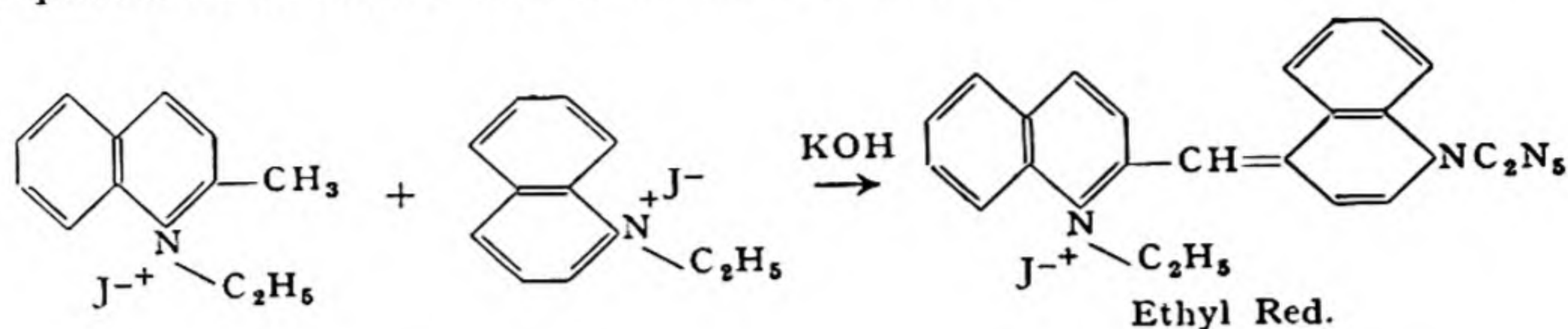
The alkalides of quinoline, quinaldine and lepidine are the starting materials for the preparation of an important group of dyestuffs to which the *cyanine* and *iso-cyanine dyes* belong (WILLIAMS, HOFMANN, HOOGEWERFF and VAN DORP, KÖNIG et al.). These dyestuffs are used as sensitisers in the manufacture of panchromatic photographic plates and films.

Cyanine Blue is produced by the action of caustic alkali solution on a mixture of lepidine ethiodide and quinoline ethiodide; the latter compound is first of all converted into a pseudo-base, which is oxidised in presence of air to a *quinolone*, which then undergoes condensation with lepidine ethiodide:



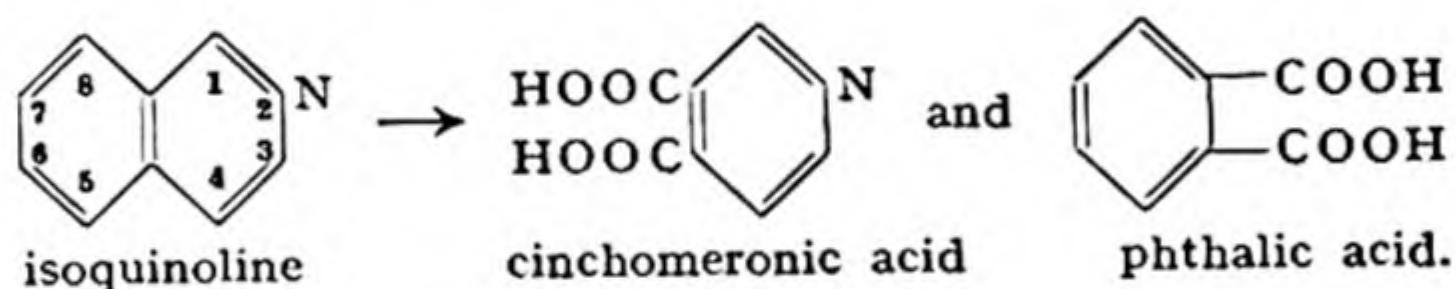
Iso-cyanine dyes are red in colour. They are produced when a methyl group in

the 2-position in a quinoline derivative reacts. *Ethyl Red*, for example, is produced from quinaldine ethiodide and quinoline ethiodide:



Isoquinoline

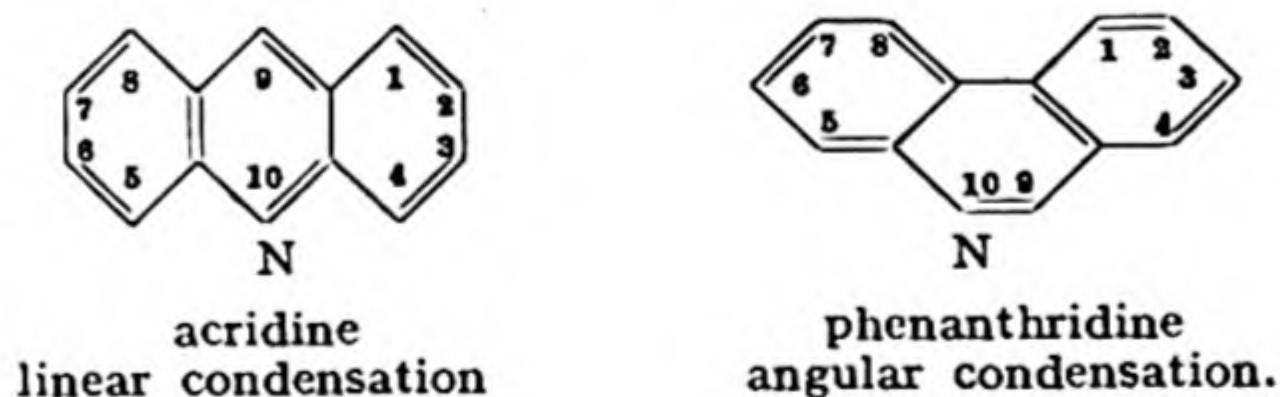
339. *Isoquinoline* C_9H_7N , occurs in coal-tar in smaller amounts than quinoline; it was isolated from this source by HOOGEWERFF and VAN DORP in the form of a sparingly soluble sulphate (1885). These investigators also established its structure. Isoquinoline is a stronger base than quinoline; it melts at 24.5° and boils at 243° . It forms quaternary salts with alkyl halides. By oxidising isoquinoline with potassium permanganate, phthalic acid and cinchomeronic acid (**336**) are produced:



The isoquinoline ring occurs in several alkaloids (**361**).

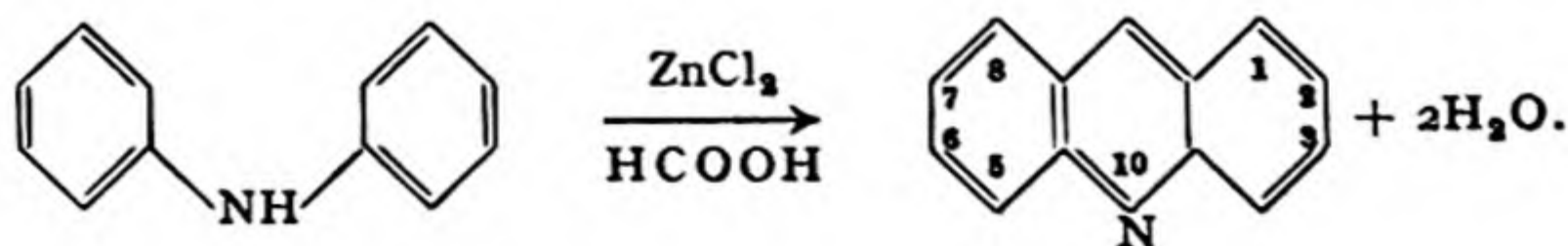
Dibenzopyridines

340. The pyridine ring can be condensed with two benzene rings in different ways:

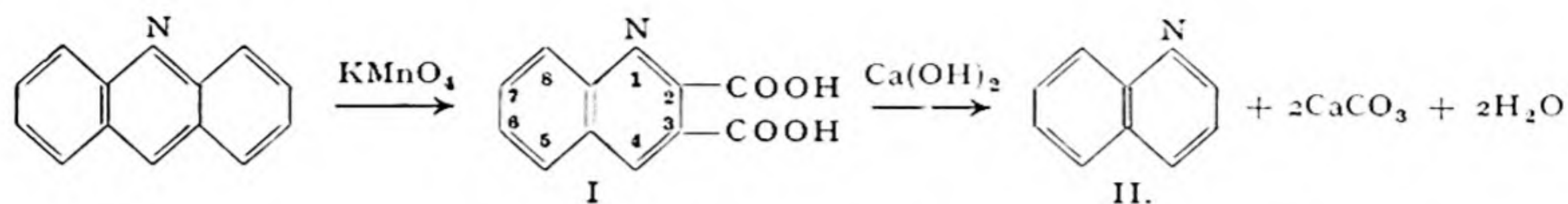


In this book discussion must be limited to *acridine* or *linear dibenzopyridine*.

Acridine $C_{13}H_9N$ occurs in small quantities in coal-tar (GRAEBE and CARO 1870). The name is derived from the irritant action which this substance exerts on the skin. The structure follows from the formation from diphenylamine and formic acid by heating with zinc chloride. The yield in this reaction, however, is very low:

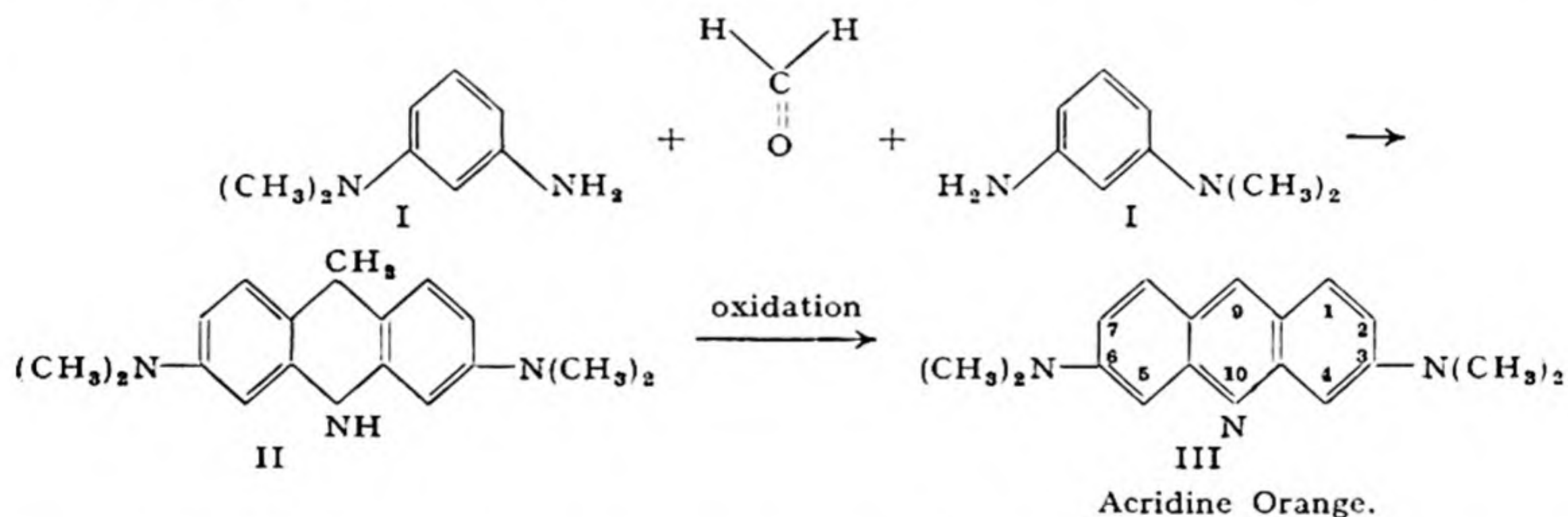


This structure is confirmed by oxidising acridine with potassium permanganate when quinoline 2,3-dicarboxylic acid (I), which gives quinoline (II) on heating with lime, is obtained:

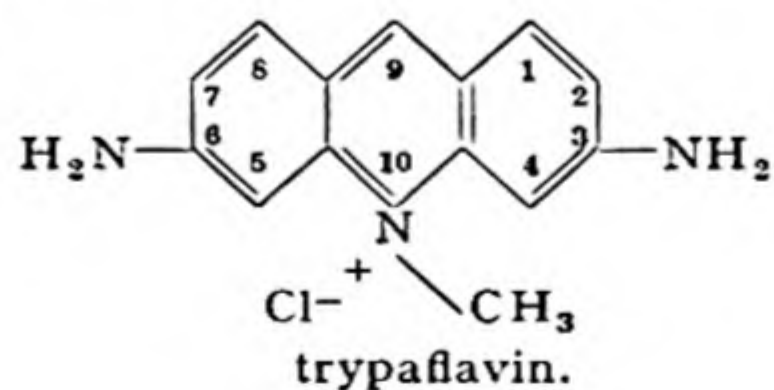


Acridine melts at 108°, easily sublimes, is volatile in steam and boils at 346°. It is sparingly soluble in water but readily soluble in alcohol and ether. Dilute solutions show a blue fluorescence. Acridine gives salts with strong acids, which are partly decomposed by boiling with water. The acridine ringsystem occurs in a number of dyestuffs.

Tetramethyl-3,6-diaminoacridine or *Acridine Orange*, which is prepared from 1-amino-3-(dimethylamino)-benzene (I) and formaldehyde, may be mentioned. In this case, a dihydro-derivative of acridine (II) is first produced and is converted by atmospheric oxidation into the dyestuff (III), which is isolated as the zinc chloride double salt and is used for dyeing cotton and silk:



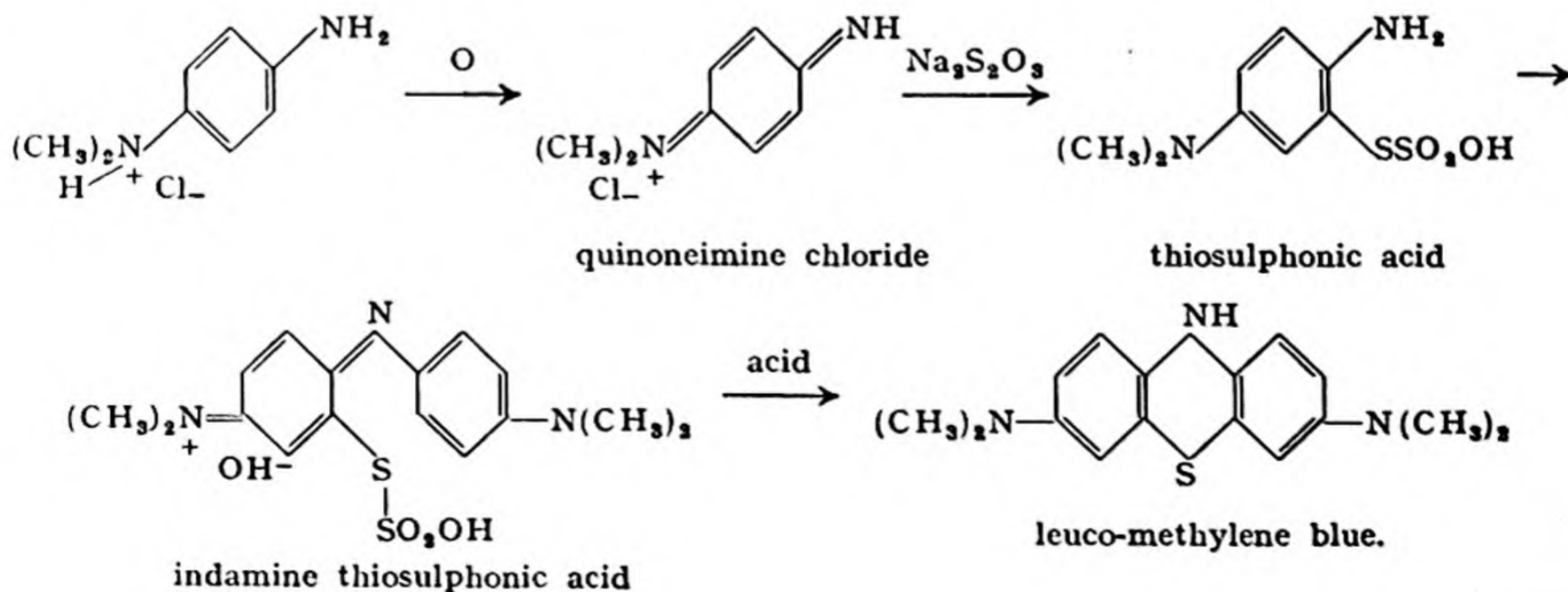
The methochloride of 3,6-diaminoacridine is used under the name of *trypanflavin* as a disinfectant in the treatment of wounds and for combatting streptococcal and staphylococcal infections (P. EHRLICH and BENDA):



SIX RING-SYSTEMS WITH TWO HETERO-ATOMS IN THE RING

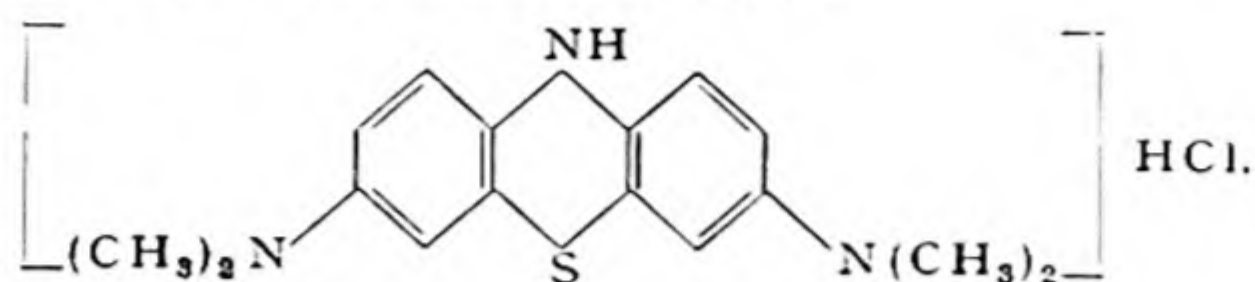
341. Compounds, in which a six-ring formed from four carbon atoms, a sulphur atom and a nitrogen atom, condensed with two benzene rings occurs, are of importance because the so called *dibenzoparathiazine* dyestuffs, which at one time found wide application for dyeing cotton, belong to this class.

Methylene Blue is produced by the so-called "thiosulphate process" in which a mixture of dimethyl-*p*-phenylenediamine and dimethylaniline is oxidised, usually with potassium bichromate, in the presence of sodium thiosulphate and zinc chloride. The process takes place very smoothly although the following stages are involved:



The dyestuff is eventually formed by oxidising the leuco-compound in acid solution.

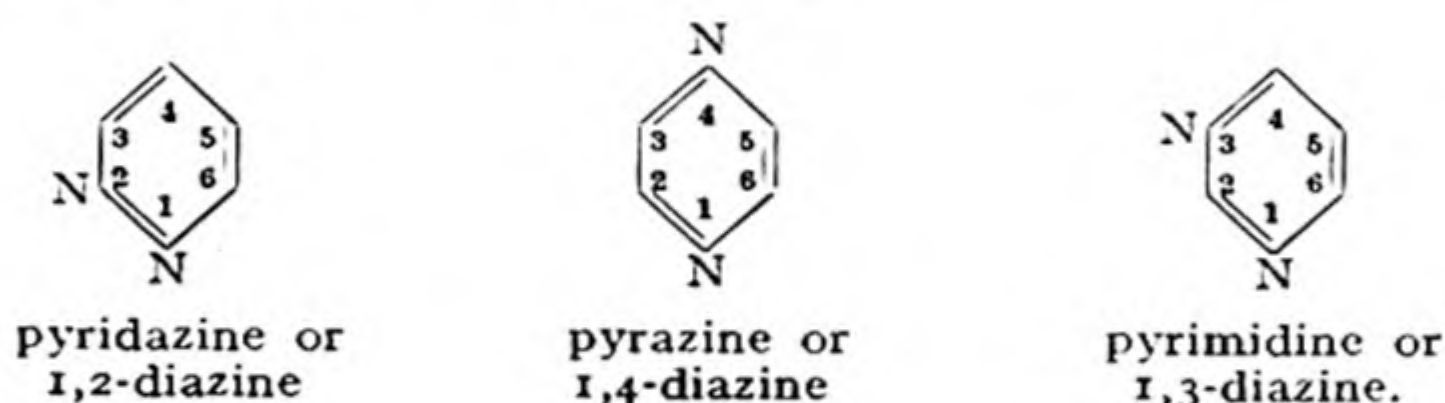
Methylene Blue crystallises with three molecules of water of crystallisation as $C_{16}H_{18}N_3SCl \cdot 3H_2O$. It is readily soluble in cold water to a deep blue solution. Methylene Blue can be easily reduced, *e.g.* with sodium hydrosulphite in alkaline solution, to give colourless *leuco-methylene blue*:



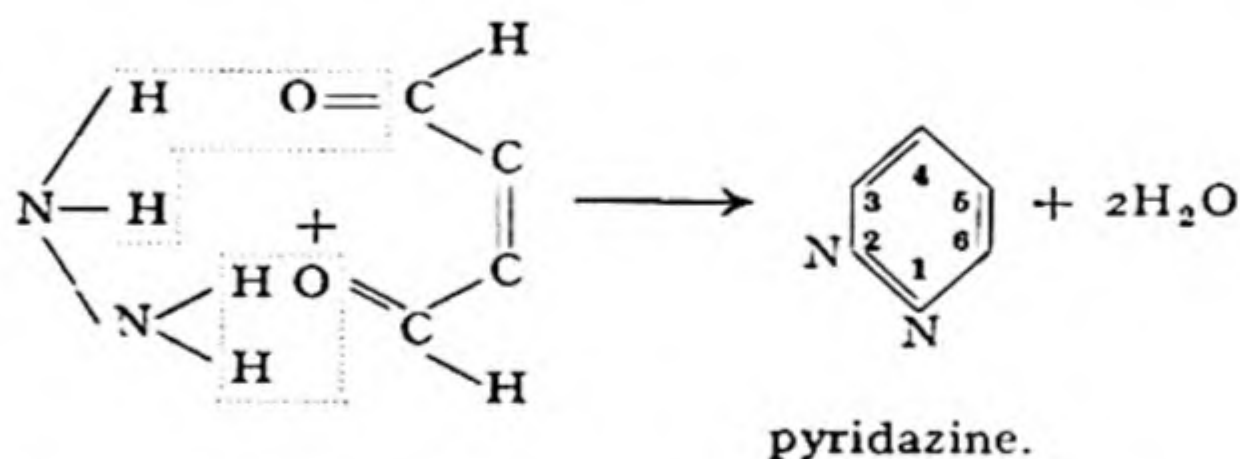
Methylene Blue is much used in microscopic investigation on cells and tissues; certain parts of animal tissues, particularly nerve tissue, is deeply stained, while other parts remain uncoloured.

(ii) DIAZINES

342. The three ring-systems forming the basis of this class of compounds contain two nitrogen atoms in the ring:

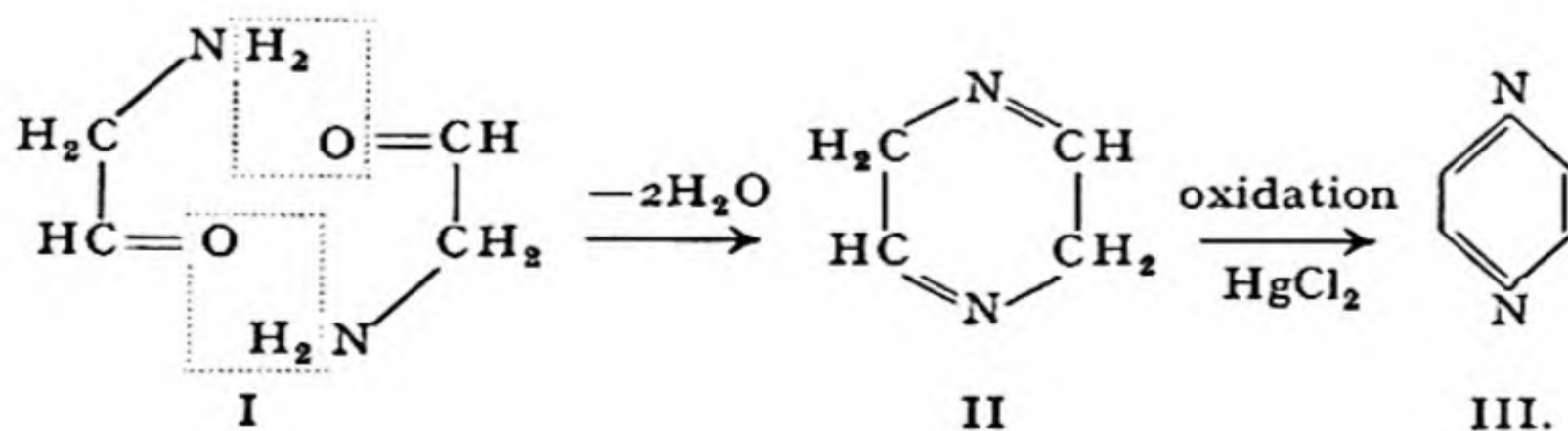


Pyridazine, $C_4H_4N_2$, can be obtained by the action of hydrazine on the dialdehyde of maleic acid:



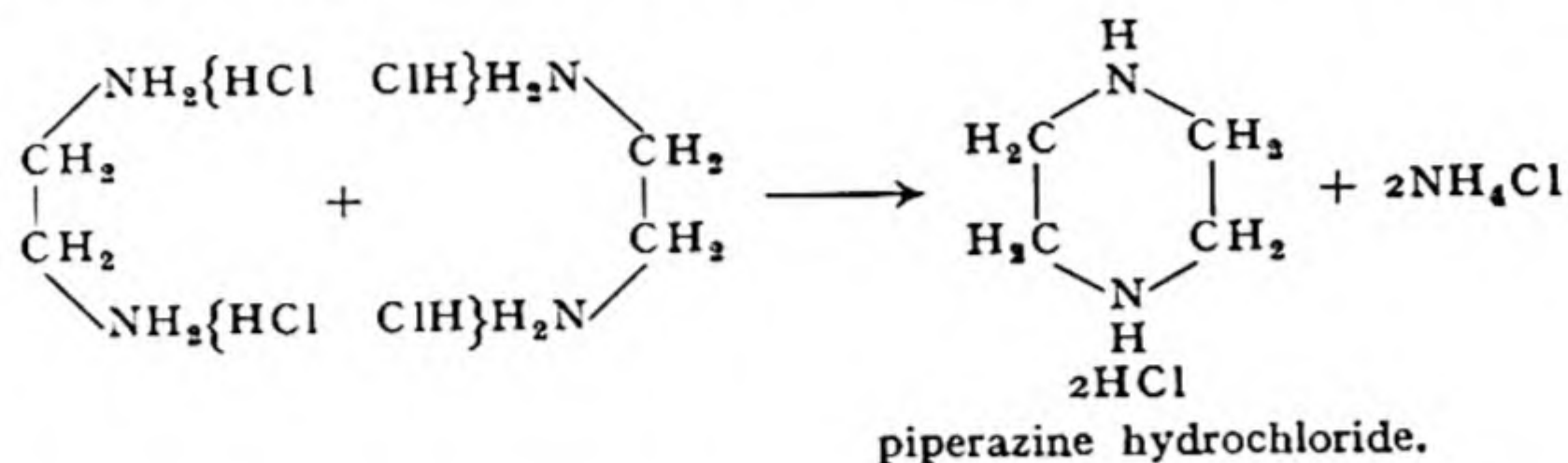
It is a basic liquid immiscible with water, boiling at 205° and possessing an odour similar to that of pyridine. The pyridazines are of little importance.

Pyrazine $C_4H_4N_2$ can be obtained by treating the hydrochloride of aminoacetaldehyde with alkali and mercuric chloride. The free aminoacetaldehyde (I) condenses in the alkaline medium to a dihydropyrazine (II), which is oxidised by the mercuric oxide to pyrazine (III):



Pyrazine sublimes very easily; it melts at $52-53^\circ$ to a colourless, highly refractive liquid boiling at 116° . It is readily soluble in water and alcohol and forms a hydrochloride $C_4H_4N_2 \cdot HCl$ with hydrochloric acid. It is oxidised by permanganate at ordinary temperatures.

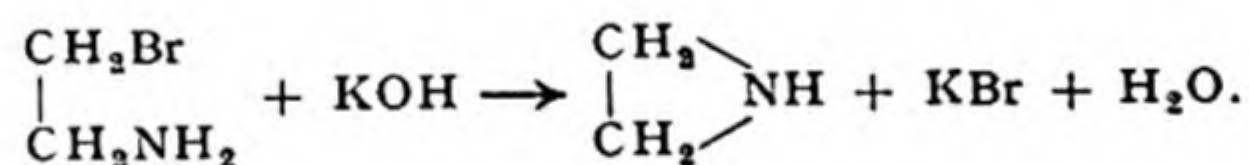
Hexahydropyrazine $C_4H_{10}N_2$ or *piperazine* (m.p. 104° , b.p. 145°) is produced in low yield by heating the hydrochloride of 1,2-diaminoethane (ethylenediamine):



The *ketopiperazines*, derivatives of piperazine, have been discussed in the section dealing with amino-acids (see 203).

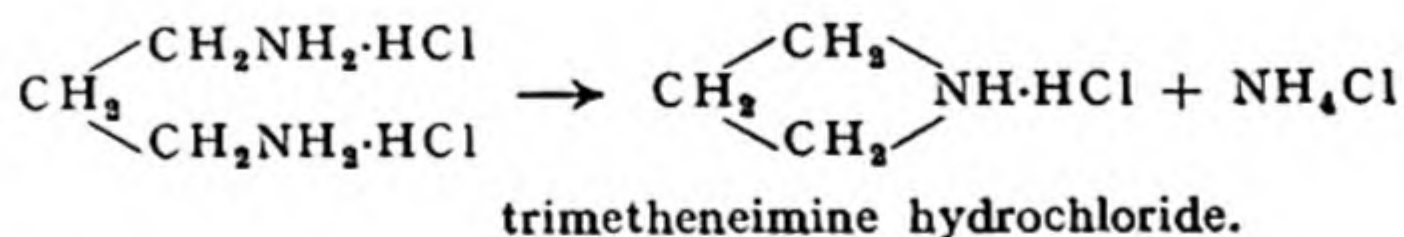
Cyclic imine

Dimetheneimine (etheneimine or ethyleneimine, a *cyclic imine*) is not produced by heating the above-mentioned salt of diaminoethane, just like ethene oxide cannot be obtained by abstracting water from ethanediol (III). As in the formation of ethene oxide from chlorethanol, so dimetheneimine can be formed by the action of potassium hydroxide on 1-bromo-2-aminoethane:

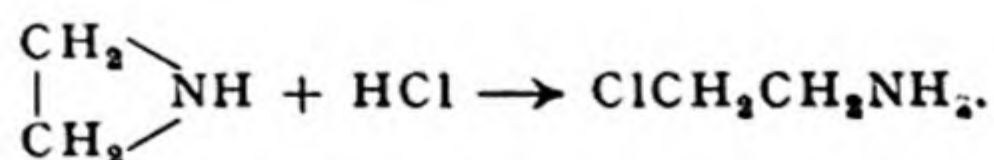


Dimetheneimine is a volatile ammoniacal base (b.p. 56°), which is readily decomposed by water.

Trimetheneimine (*trimethyleneimine*) (b.p. 63°) is produced in low yield by heating 1,3-diaminopropane hydrochloride:



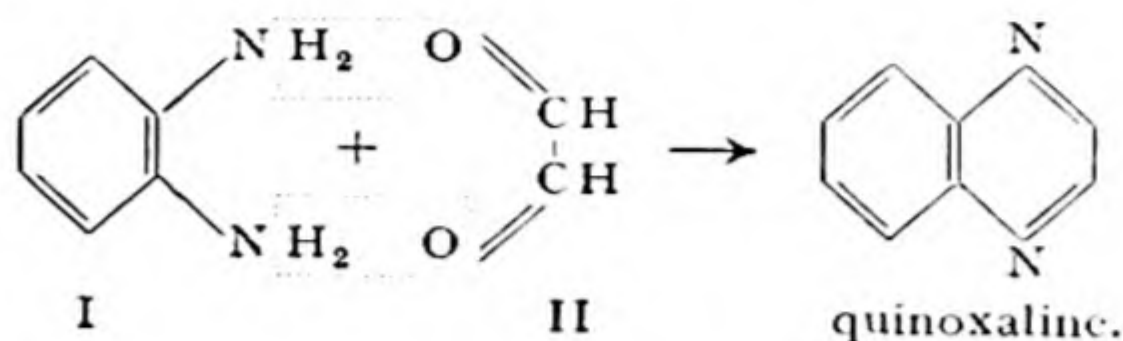
Dimetheneimine and trimetheneimine are converted into the corresponding chloramines when evaporated down with hydrochloric acid, the ring being opened:



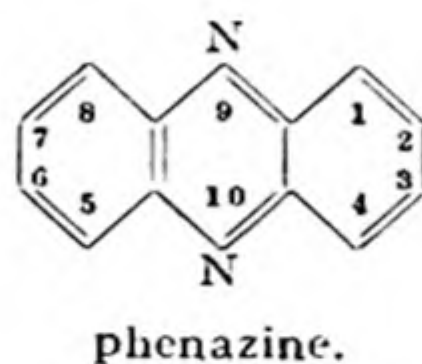
On the other hand, tetrametheneimine or pyrrolidine (314) and *pentametheneimine* or piperidine (332) are stable compounds. Similar reactions occur with these cyclic imines as with the alkene oxides (III).

(a) *Quinoxalines*

343. A number of ring-systems are known in which a pyrazine-ring condensed with a benzene-ring occurs. These are called quinoxalines and have been mentioned already in **238**. Quinoxaline itself is produced from *o*-diaminobenzene (I) and glyoxal (II):

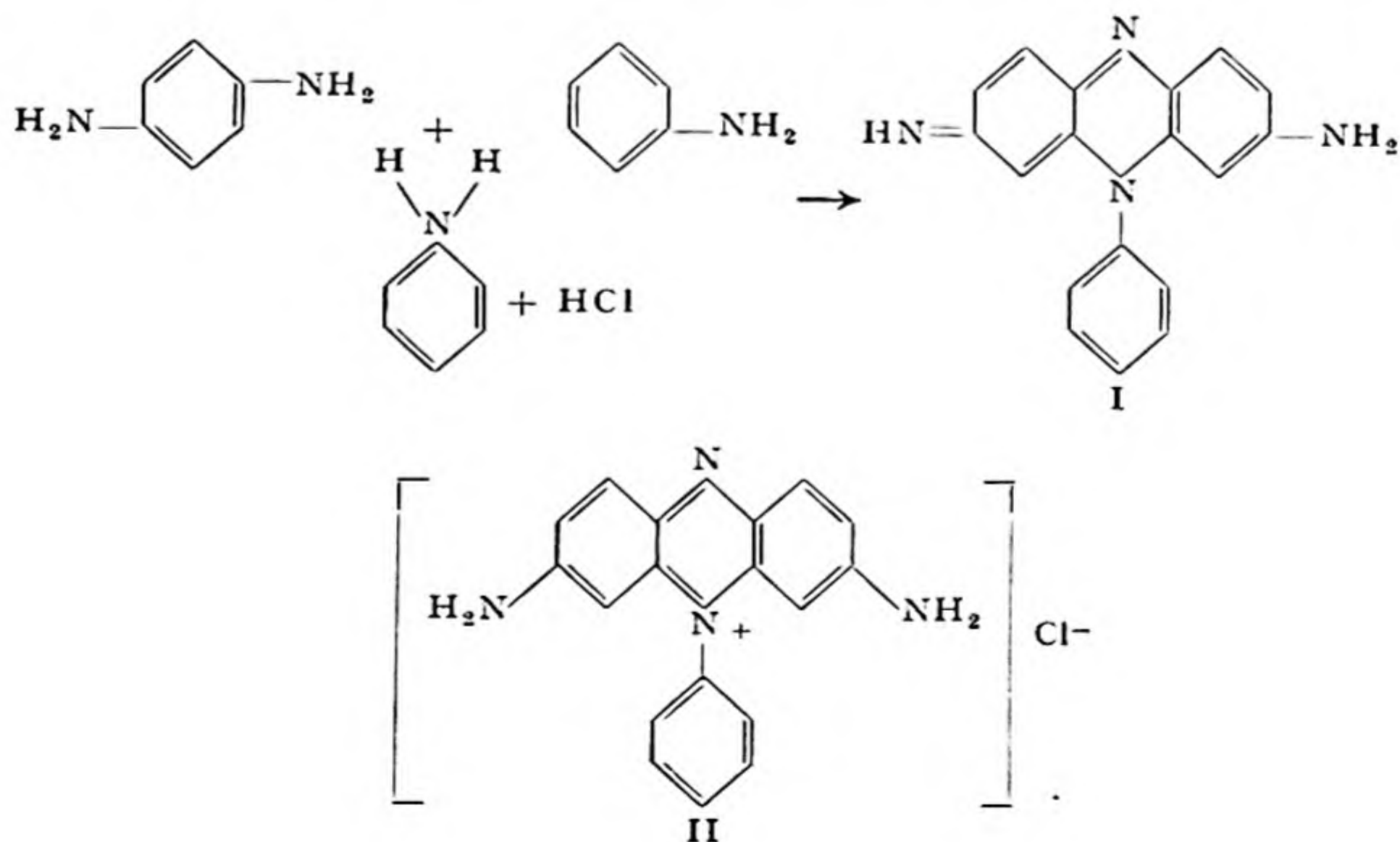
(b) *Phenazines*

Some important dyestuffs are derived from *phenazine*, in which a pyrazine ring is condensed with two benzene rings:



In this connection, the *safranine dyestuffs* may be mentioned. These compounds, used for dyeing cotton and silk, are diamino-derivatives of *N*-phenylphenazonium salts.

By oxidising a mixture of 1 mol. of *p*-phenylenediamine and 2-mols. of aniline with a warm neutral solution of potassium bichromate, yellowish red *phenosafranine* (I) in which a *para*-quinonoid ring occurs, is produced. It is not yet known what intermediate products are formed in this very peculiar method of formation:



The hydrochloride with an *ortho*-quinonoid structure is shown in II.

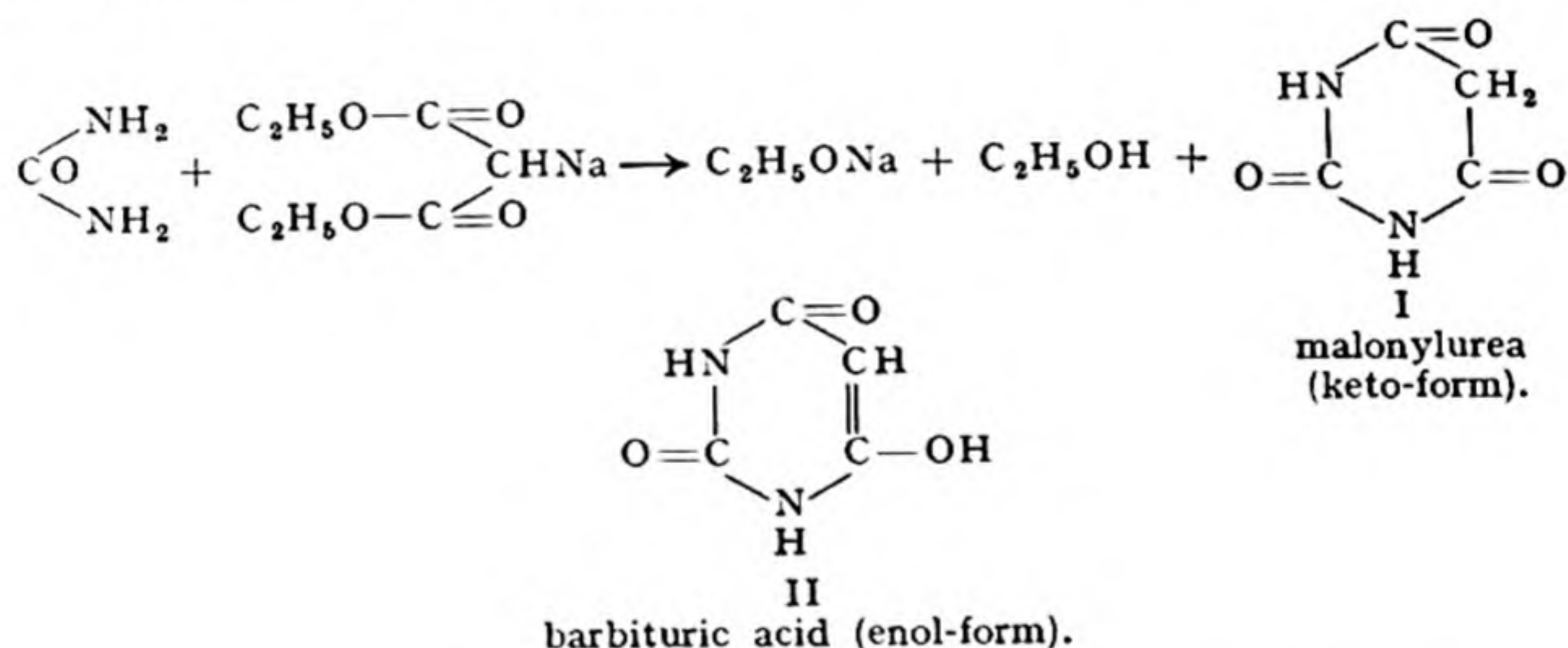
Derivatives of phenosafranine in which the hydrogen atoms in the amino-groups are replaced by alkyl groups or in which the benzene nuclei carry substituted methyl groups, are also used as dyestuffs.

(c) *Pyrimidine and its derivatives*

344. The pyrimidine group is of very great importance because this ring-system occurs in a number of compounds, which are distributed throughout the animal and vegetable kingdoms, including the *purine* derivatives (347), fission products of nucleic acids (349), vitamin-*B*₁, (345) and vitamin-*B*₂ (350).

The grouping $\text{>N}-\text{C}-\text{N}<$ occurs in the pyrimidine ring and also in urea (151) and the amidines (78). The latter compounds may be used therefore in the synthesis of pyrimidine derivatives.

By warming urea with ethyl sodium malonate in alcoholic solution, *malonylurea* or *barbituric acid*, which may be regarded as a triketo-derivative of hexahydropyrimidine, is produced:

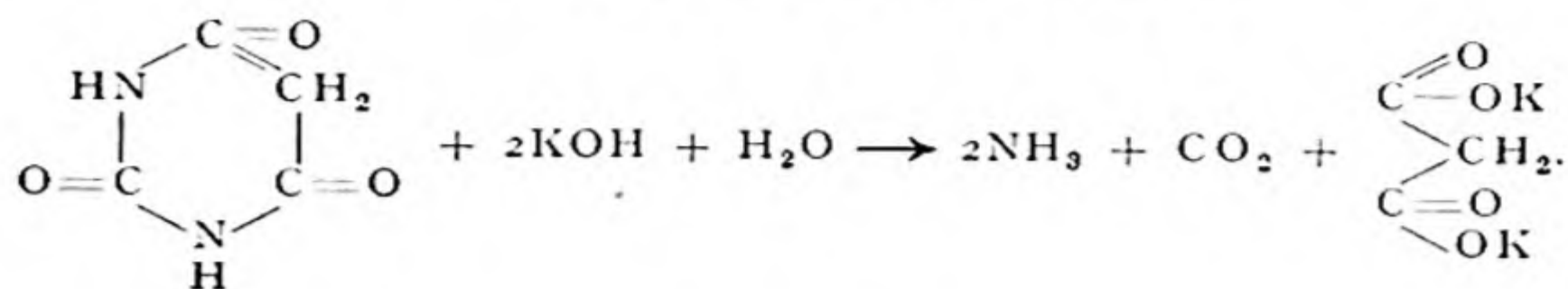


Barbituric acid is sparingly soluble in water, decomposes on melting, is a stronger acid than acetic acid and behaves like a mono-basic acid.

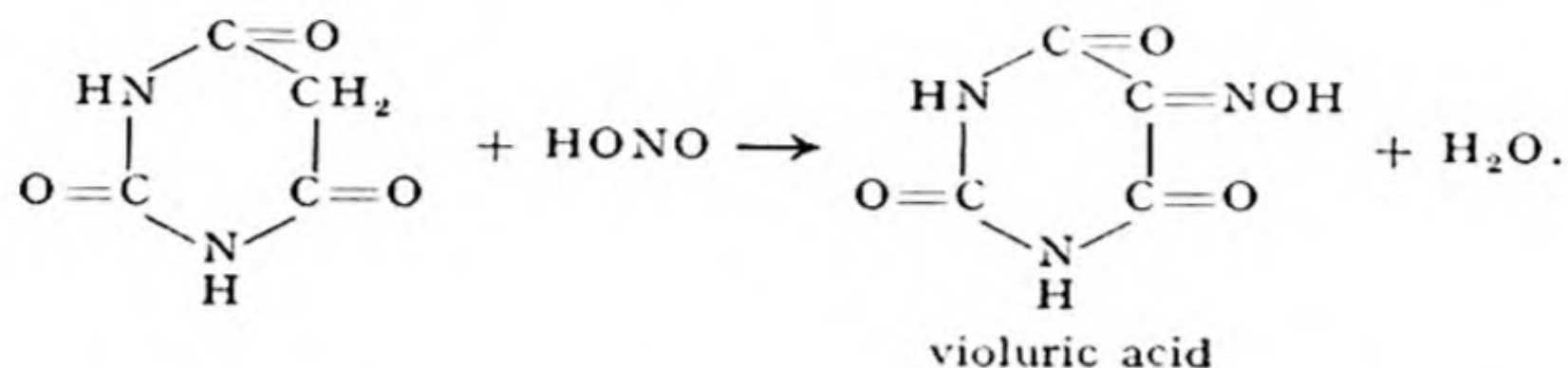
On the other hand, *diethylbarbituric acid* has only very feeble acid properties; the acid character of barbituric acid must therefore be ascribed to enolisation of the grouping $-\text{CH}_2-\text{CO}- \rightarrow -\text{CH}=\text{COH}-$ as shown in II.

Barbituric acid can also be considered as the *ureide* of malonic acid, a ureide being a derivative of urea in which one hydrogen atom in each of the two NH_2 -groups is replaced by an acyl radical.

The bonds between the $-\text{NH}-$ and $-\text{CO}-$ groups in barbituric acid are easily broken by alkaline hydrolysis; on boiling with alkalis, ammonia, carbon dioxide and an alkali malonate are produced:



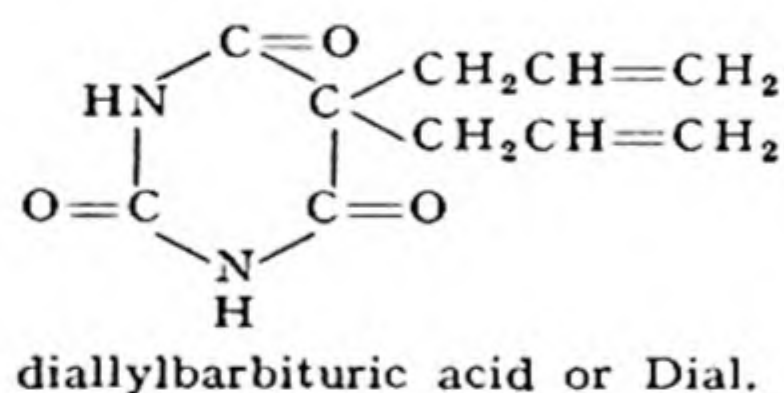
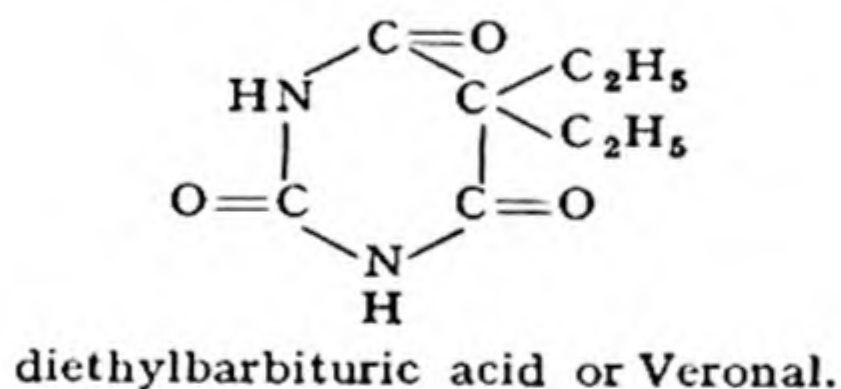
In barbituric acid, as in malonic acid, a methylene group is situated between two carbonyl groups so that the hydrogen atoms in this methylene group become very reactive. Thus isonitrosobarbituric acid or *violuric acid* is produced by the action of nitrous acid on malonylurea:



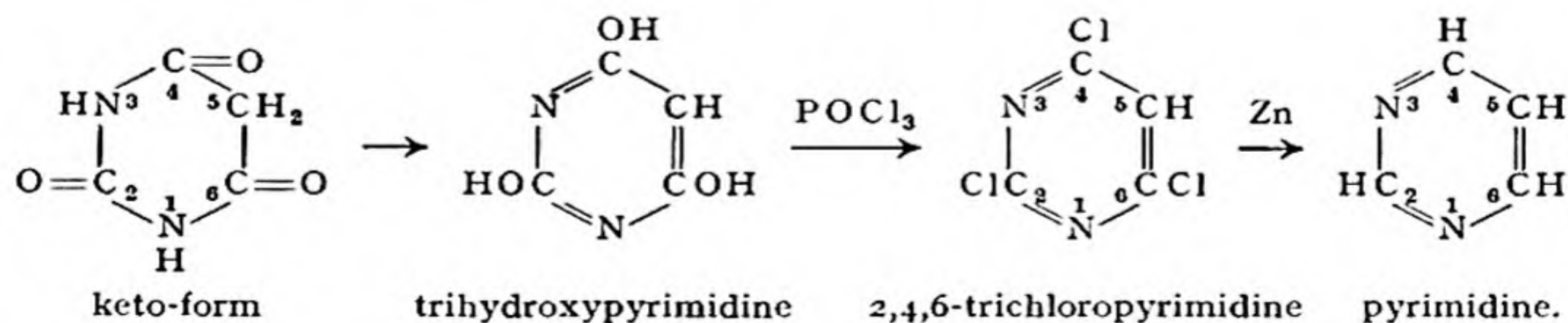
This compound is colourless but its metallic salts are deeply coloured. A blue and a red potassium salt, a violet barium salt, a red and a deep yellow lithium salt, for example, are known. No satisfactory explanation for the colour of these salts has yet been given.

Diethylbarbituric acid, $\text{C}_8\text{H}_{12}\text{O}_3\text{N}_2$, which is used under the name of *Veronal* as a soporific (E. FISCHER and VON MERING) is obtained by condensing an ester of diethylmalonic acid with urea in alcoholic solution with the help of sodium ethylate.

Several other derivatives of barbituric acid substituted on the carbon atom are used as soporifics, *e.g.* diallylbarbituric acid or *Dial*:

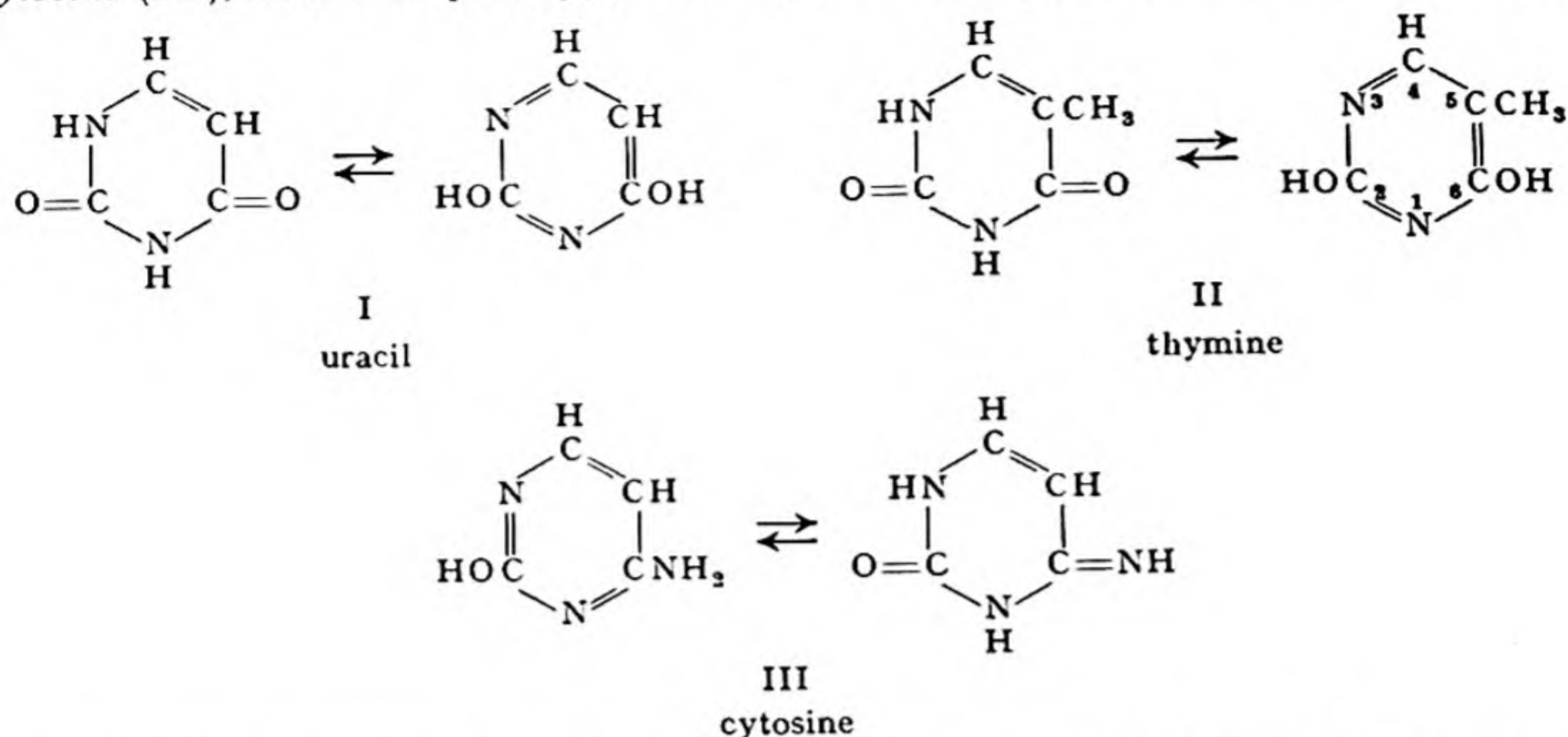


Pyrimidine. By the action of phosphorus oxychloride on barbituric acid, 2,4,6-trichloropyrimidine is produced, which can be reduced to pyrimidine with zinc dust (GABRIEL). It may be assumed in this reaction, that the barbituric acid reacts in a tautomeric form as trihydroxypyrimidine:

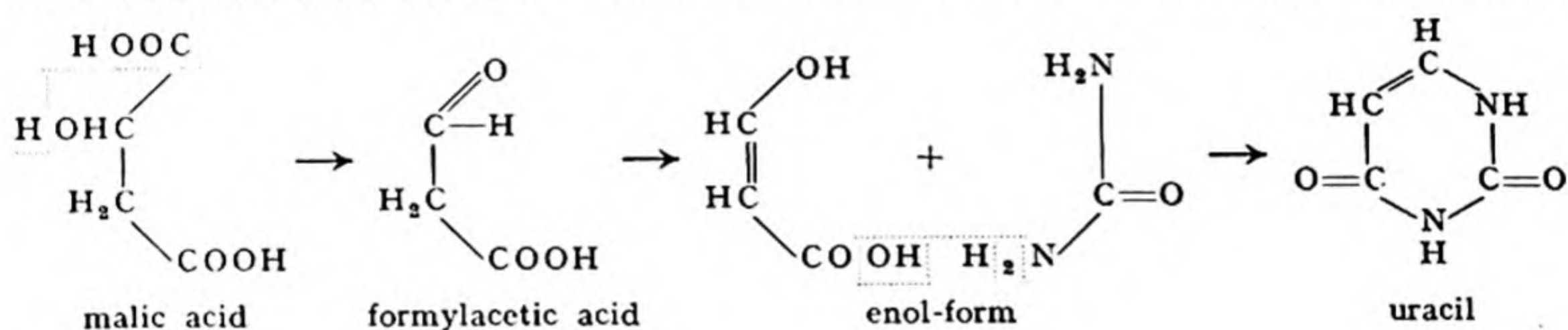


Pyrimidine melts at 20–22°, is colourless and boils at 124°; the liquid is miscible with water and has a neutral reaction.

2,6-Dihydroxypyrimidine or *uracil* (I), its methyl derivative, *thymine* (II) and *cytosine* (III), an aminohydroxypyrimidine, are fission products of nucleic acids (349):



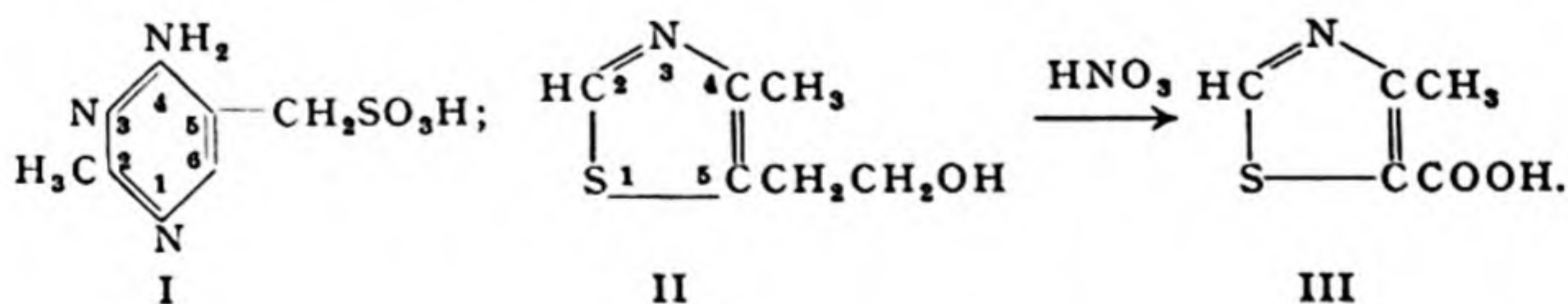
Uracil can be prepared synthetically from malic acid and urea by the action of fuming sulphuric acid. It must be assumed that formylacetic acid is first of all produced from the malic acid and this then combines with urea to form a pyrimidine ring:



Thiamin, aneurin or vitamin-B₁

345. The structure of this compound (306) has been established by the researches of R. WILLIAMS and his collaborators and has been confirmed by synthesis.

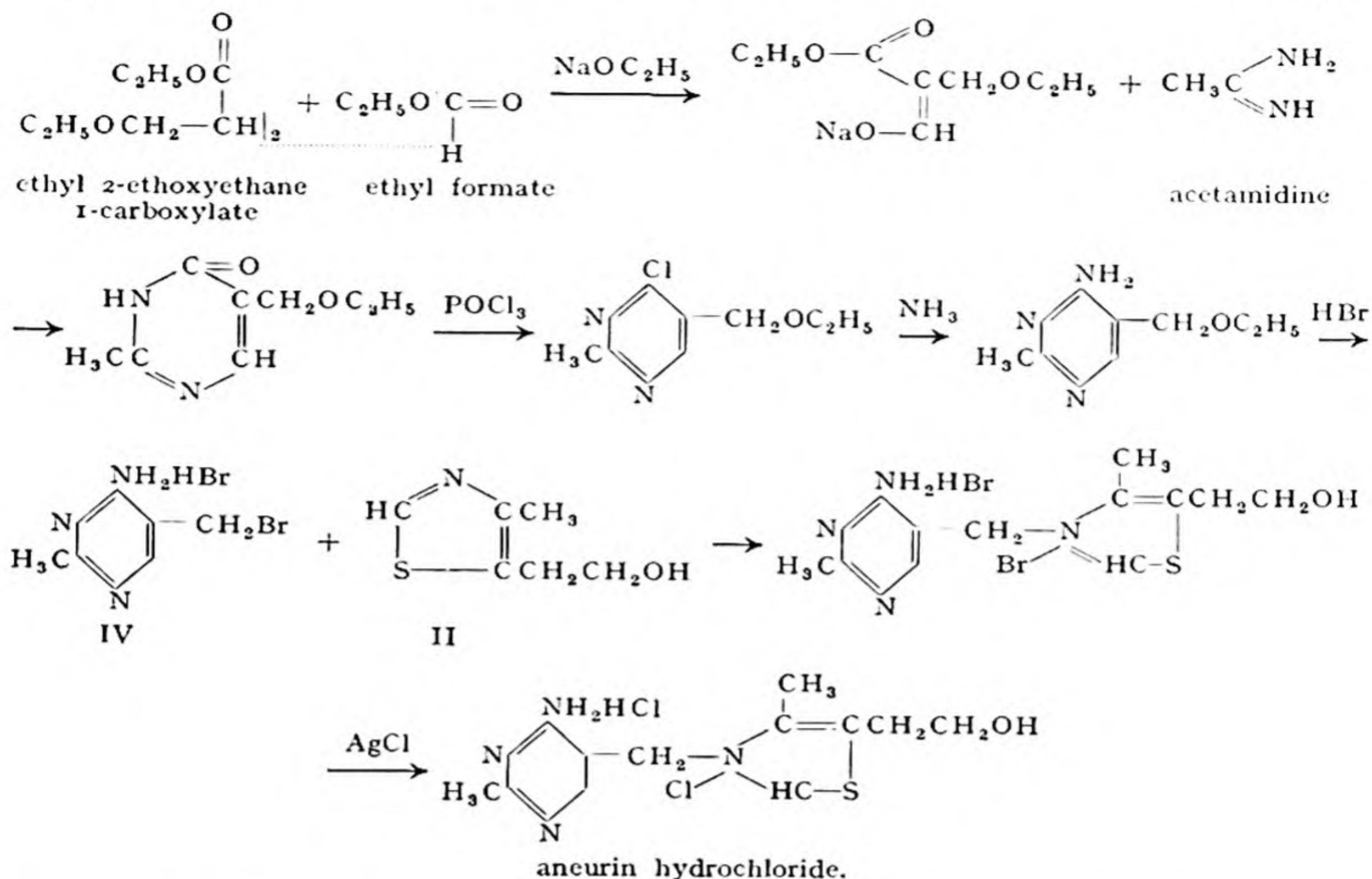
By treating thiamin hydrochloride $\text{C}_{12}\text{H}_{18}\text{ON}_4\text{Cl}_2\text{S}$ with an aqueous solution of sodium sulphite and sulphurous acid, the molecule undergoes fission into a pyrimidine derivative I and a thiazole derivative II:



4-Methyl-5-β-hydroxyethylthiazole (II) is oxidised by nitric acid to *4-methylthiazole 5-carboxylic acid* (III), which is also obtained when aneurin is oxidised. From this it appears that aneurin contains a thiazole-ring (322). This is the first example of a naturally occurring product containing this ring-system.

The SO₃H group in I is derived from the sulphurous acid used in the fission.

For the synthesis of aneurin the pyrimidine derivative IV was prepared:



This compound IV adds on 4-methyl-5-β-hydroxyethylthiazole (II), which is also prepared synthetically, with the formation of a quaternary *thiazolinium salt*. When the ionogenically bound bromine in this compound is replaced by chlorine, *aneurin hydrochloride* is produced. This synthetically produced substance was found to be identical with the natural product as regards physiological action and its absorption spectrum.

Iminazolopyrimidines or purine derivatives

346. To this group belong many compounds of great importance from the physiological point of view, such as uric acid and various fission products of nucleic acids, as well as a number of vegetable bases such as xanthine, theobromine, caffeine, adenine, etc., which are related chemically to uric acid. This acid therefore will be discussed first.

Uric acid or *acidum uricum* $\text{C}_5\text{H}_4\text{O}_3\text{N}_4$ was observed as early as 1776 by both SCHEELE and BERGMANN as a constituent of gall-stones and of urine. Under normal conditions an adult person excretes about 0.6 gr. every 24 hours. The excrement of birds and reptiles on the other hand consist mainly of uric acid; consequently guano and the excrement of snakes are suitable material from which to prepare this acid.

This colourless, crystalline compound decomposes on heating without melting, is very sparingly soluble in water (about 1 part in 40,000 at 18°)

but readily soluble in concentrated sulphuric acid. It is a weak acid ($k = 0.00015$) from which primary and secondary salts, called *urates*, are known.

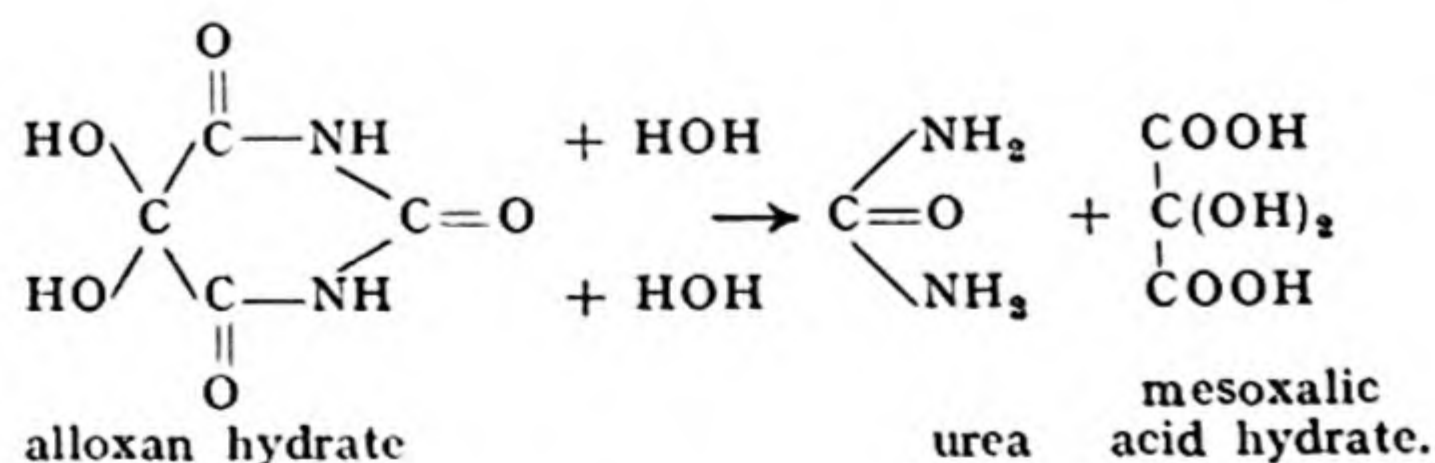
The primary salts, of which sodium and ammonium urate occur as deposits in urine, are very sparingly soluble in water.

Secondary sodium urate $(C_5H_2O_3N_4)Na_2 \cdot H_2O$, dissolves to the extent of about 1 % in cold water; the solution reacts alkaline due to hydrolysis.

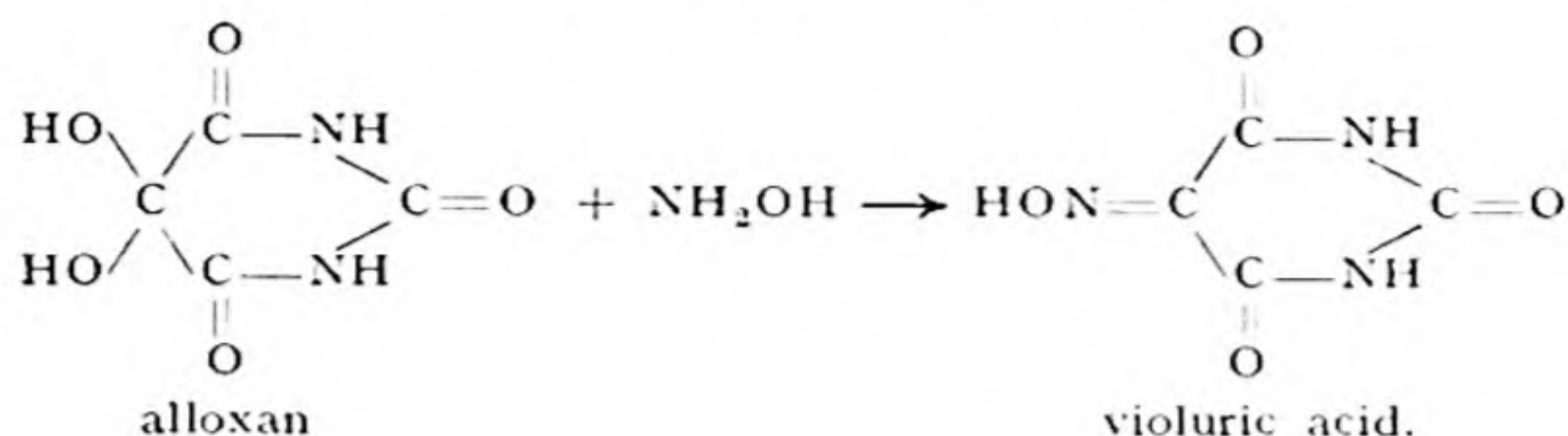
Murexide reaction. When uric acid is evaporated down with dilute nitric acid and the residue is moistened with ammonia, a reddish purple substance, *murexide*, having the composition $C_8H_8O_6N_6$, is produced; some other purine derivatives also give this reaction.

Structure of uric acid. The first researches on this subject by LIEBIG and WÖHLER date from 1837; in the course of the 19th and 20th centuries the structure of uric acid and related compounds had been established by numerous experiments carried out, for example, by A. VON BAEYER, E. FISCHER, E. GRIMAU, R. BEHREND, W. TRAUBE, A. BILTZ, and methods had been found for synthesising these compounds. By completely methylating uric acid, *tetramethyluric acid* is obtained; when this compound is heated with hydrochloric acid, the combined nitrogen is split off as methylamine hydrochloride. Since no ammonium chloride is observed, each of the nitrogen atoms in uric acid must be attached to one hydrogen atom; these hydrogen atoms are replaced by methyl groups during the methylation. Uric acid can be easily oxidised in both acid or alkaline media. By oxidation with strong nitric acid or with chlorine in acetic acid, colourless *alloxan hydrate* $C_4H_2O_4N_2 \cdot H_2O$ is produced from which anhydrous *alloxan* $C_4H_2O_4N_2$, m.p. 250° , is obtained by heating in a high vacuum. This compound is yellow in colour (compare in this connection the yellow ester of mesoxalic acid and the colourless hydrate 148).

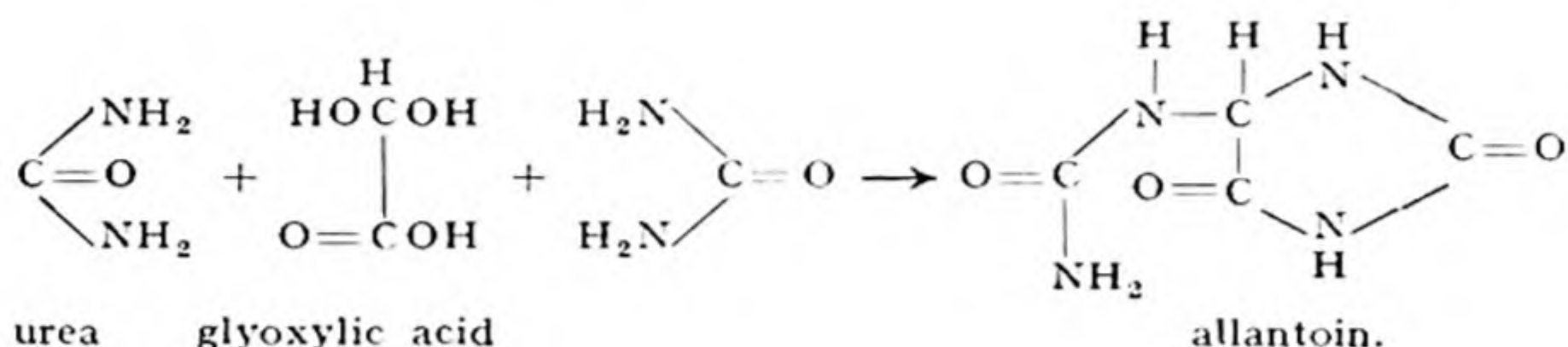
On alkaline hydrolysis of alloxan hydrate there is produced urea and a salt of mesoxalic acid, so that alloxan is considered to be the ureide of mesoxalic acid, *mesoxalylurea*:



The structure of alloxan is confirmed by the formation of violuric acid (344) by the action of hydroxylamine:

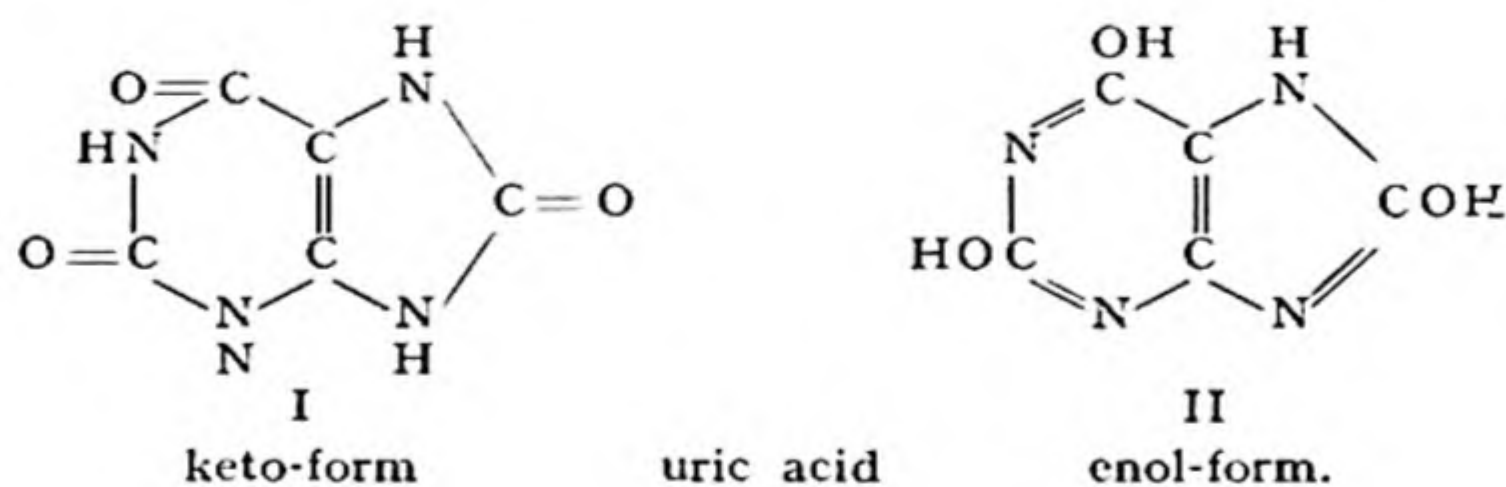


By the action of permanganate on sodium urate in alkaline solution followed by acidification with acetic acid, there is produced *allantoin* $\text{C}_4\text{H}_6\text{O}_3\text{N}_4$, m.p. $238\text{--}240^\circ$. This compound is also obtained by heating glyoxylic acid with urea; this reaction establishes its structure (GRIMAUX):

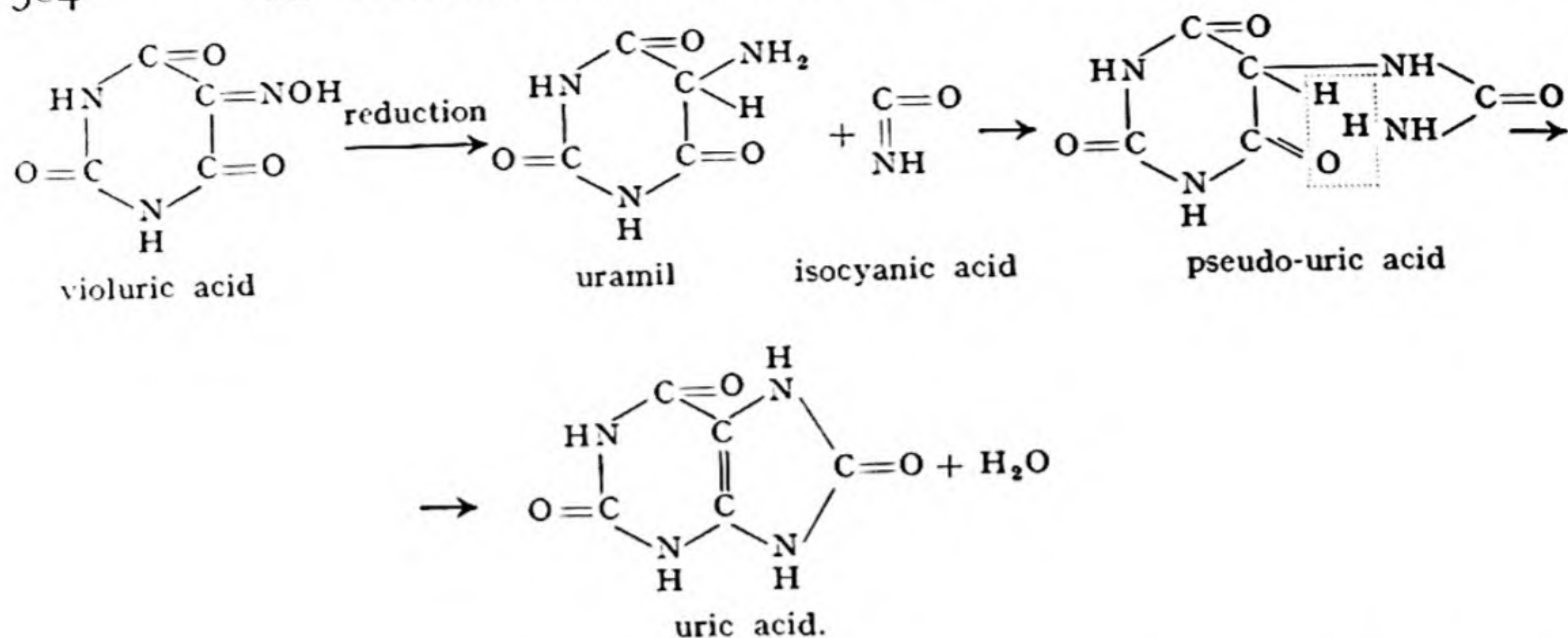


From the formation of allantoin it follows that the atom grouping of urea, viz. —N—C—N— , occurs twice in the uric acid molecule; the formation of alloxan points to the presence of a pyrimidine-ring in uric acid.

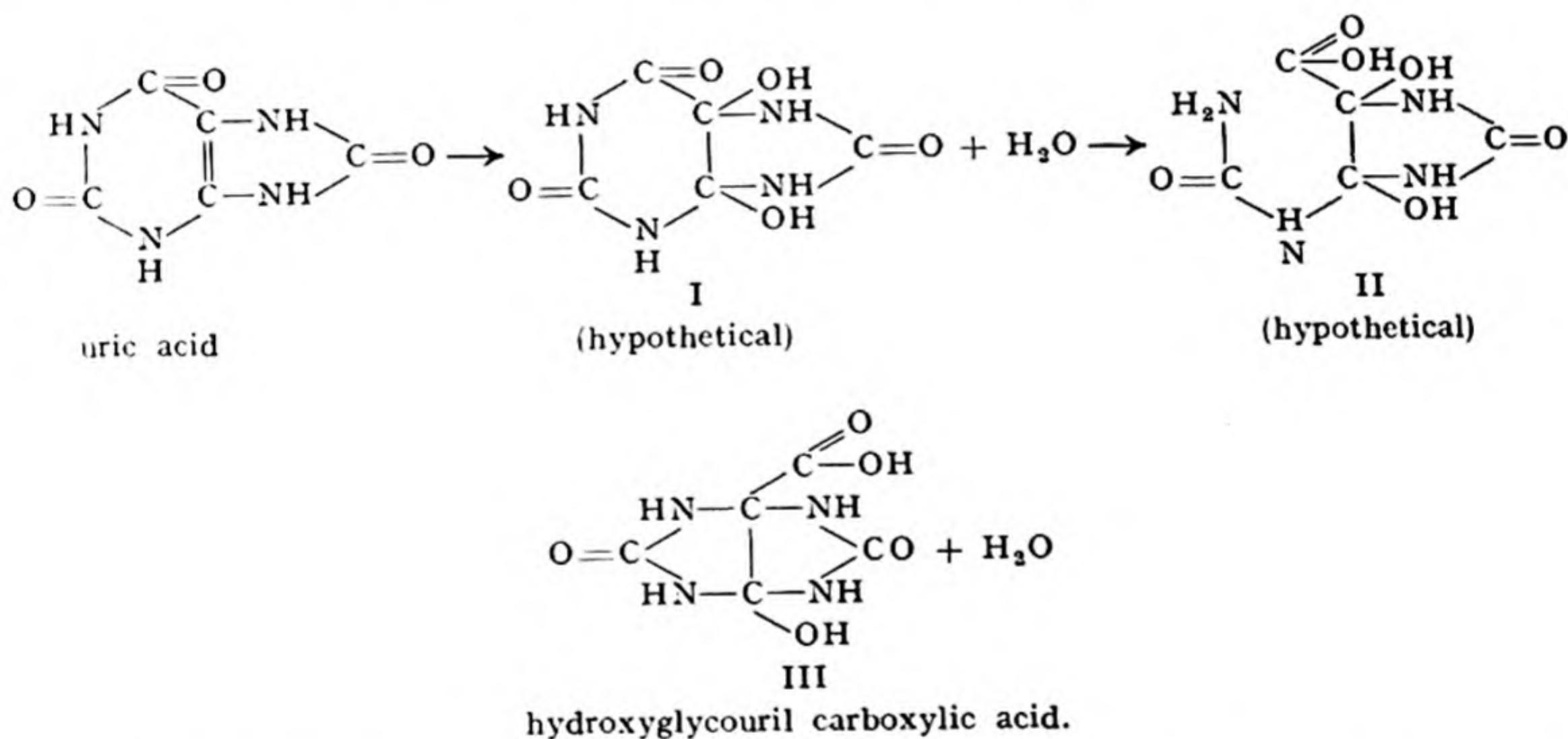
The structural formula I, which can also be written in the tautomeric form II, and which was put forward in 1875 by MEDICUS before sufficient experimental evidence was available to prove it, takes all these facts into account:



This formula is confirmed by the following syntheses. By reducing violuric acid, aminobarbituric acid or *uramil* is produced. When this compound is treated with potassium cyanate and water, a molecule of isocyanic acid (155) is added and *pseudo-uric acid* $\text{C}_5\text{H}_6\text{O}_4\text{N}_4$, is produced. When the latter is heated with hydrochloric acid, water is split off and uric acid is produced:



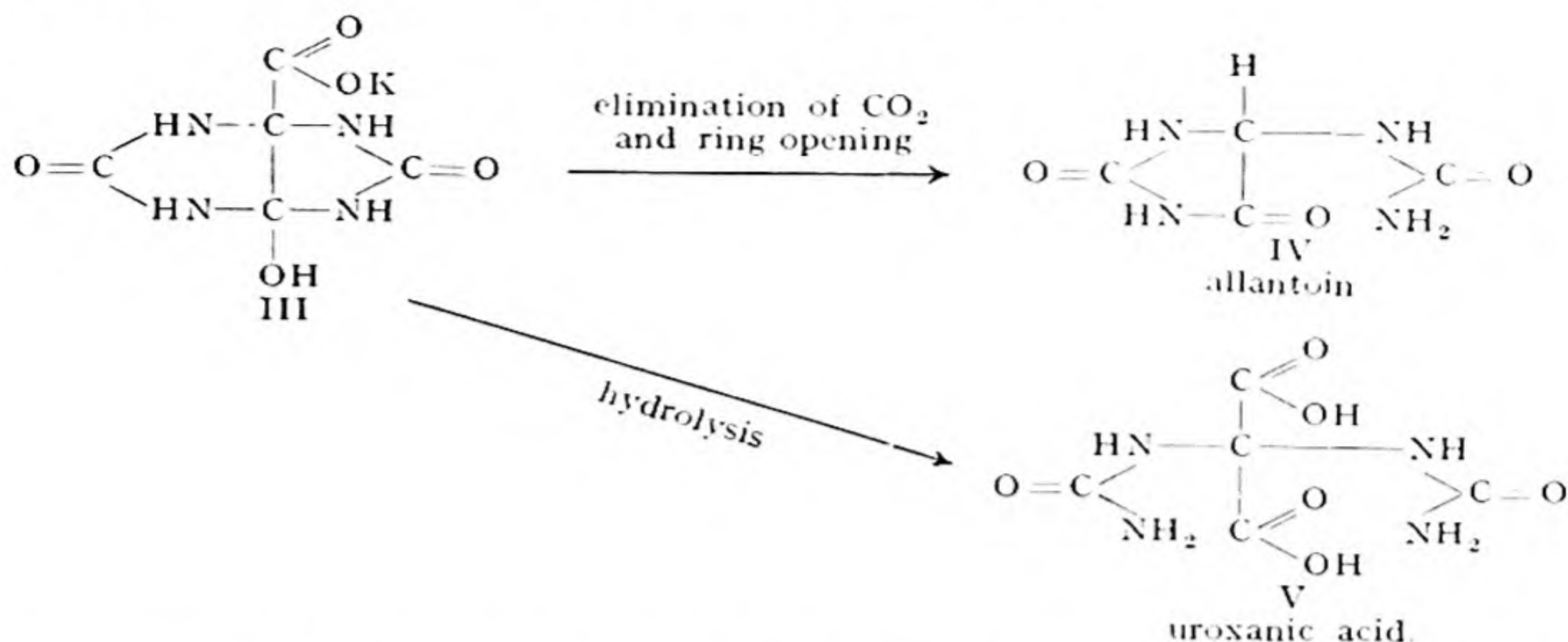
According to this structural formula, uric acid contains the pyrimidine ring system (344) and that of iminazole (324); the iminazole ring is also present in allantoin. Allantoin is produced in the oxidation of uric acid by a roundabout route. The course of this reaction must in all probability be represented as follows:



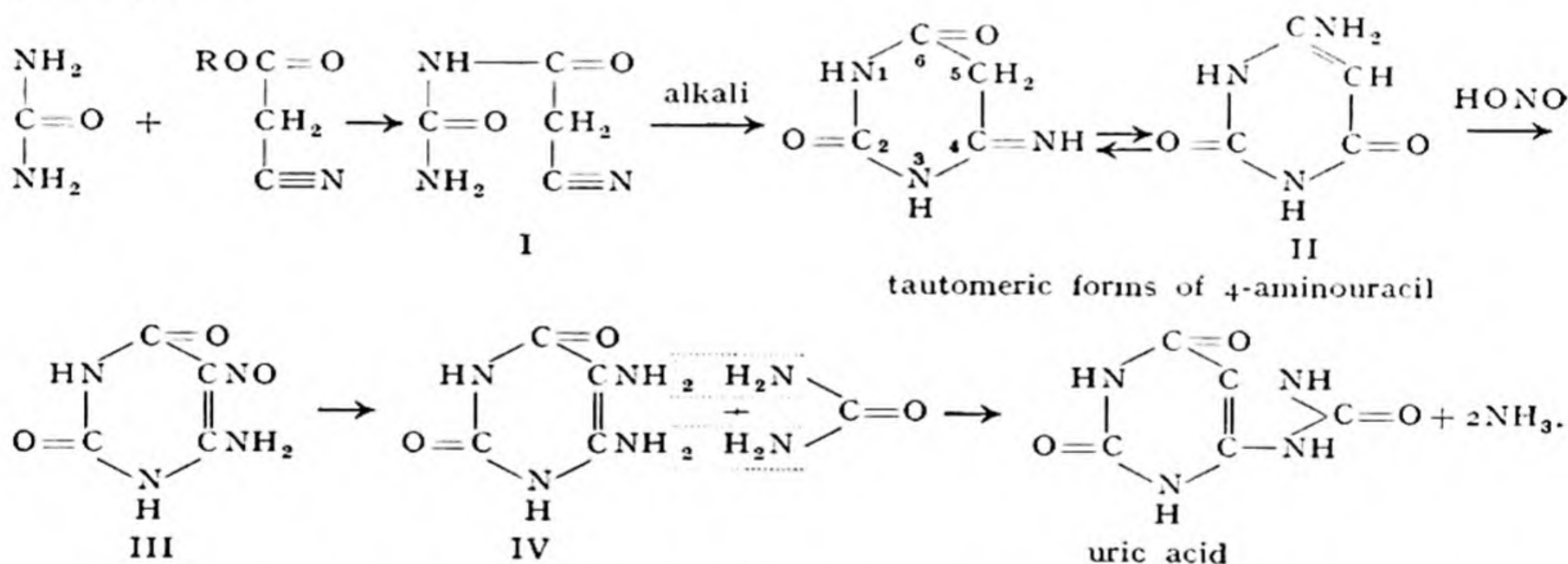
Via two hypothetical intermediates I and II, *hydroxyglycouril carboxylic acid* (III) is produced and can be isolated as the silver salt if the oxidation is carried out with alkaline permanganate at low temperatures. The alkali salt of III can then pass over either into *uroxanic acid* or *diuridomalononic acid* (V) or into *allantoin* (IV). Oxidation of uric acid in strongly alkaline media produces the potassium salt of uroxanic acid (V):

Allantoin is formed in animal tissues and organs by the enzymatic oxidation of uric acid. It occurs in the urine of carnivores and also in many plants.

TRAUBE's *synthesis of uric acid* (1900). By condensing ethyl cyanoacetate with urea, cyanoacetylurea (I) is produced, which is converted into (See formula pag. 585).

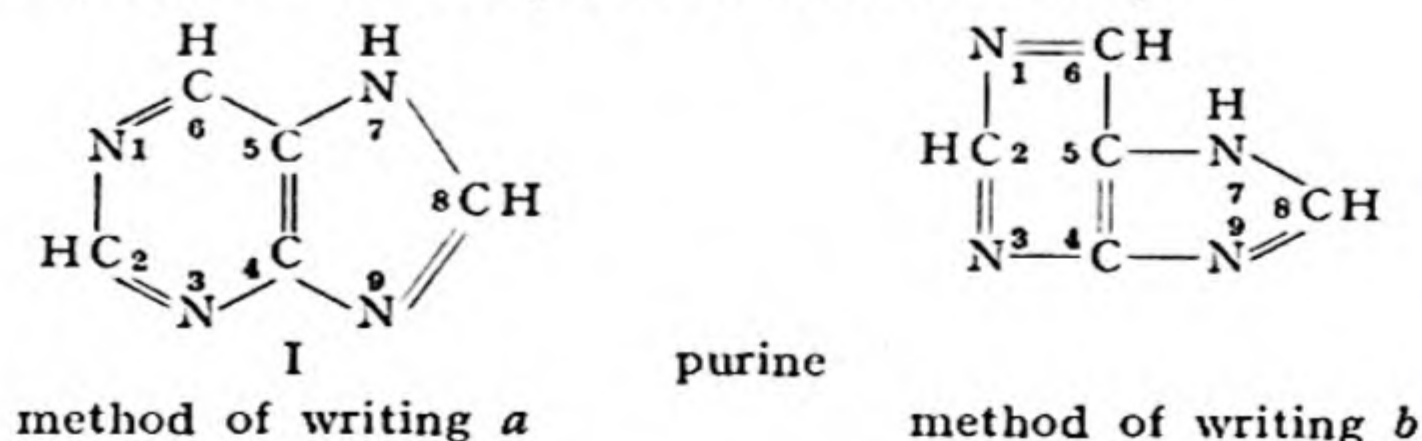


4-aminouracil (II) by the action of alkali. This compound reacts with nitrous acid giving a nitroso-derivative (III), which can be reduced to 3,4-diaminouracil (IV). When the latter is fused with urea, uric acid is produced in good yield:



Different purine derivatives may be prepared by varying the reagents in this synthesis.

347. Purine or iminazolopyrimidine. By imagining the formula for uric acid written in the tautomeric form and the hydroxyl groups replaced by hydrogen atoms, then a compound (I) is produced, which may be considered as the ultimate reduction product of uric acid and for which E. FISCHER suggested the name purine (derived from *purum* and *uricum*):

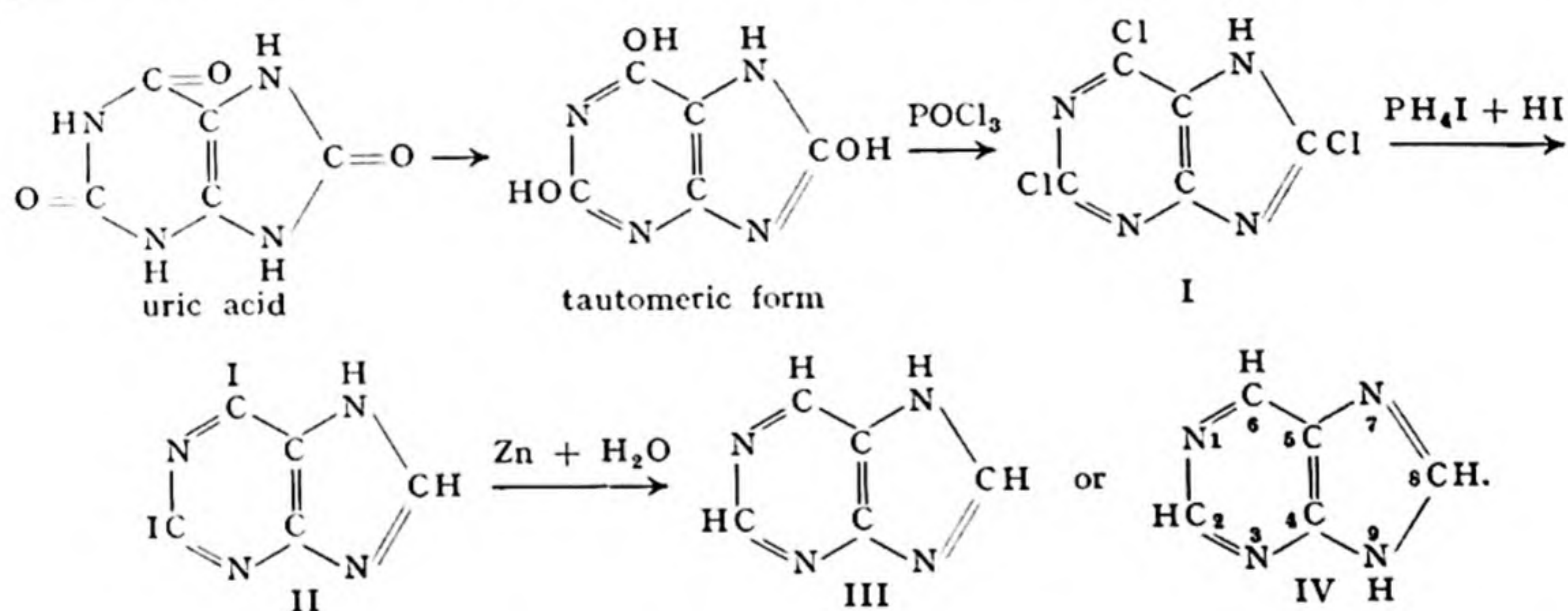


The method of numbering the carbon and nitrogen atoms was suggested by E. FISCHER and has been generally adopted although it is not in accordance with the rules laid down for heterocyclic systems.

The method of writing *a* emphasises that the iminazolopyrimidine ring-system is similar to the ring-systems of indole (315) and coumarone (312), in which a six-ring is again condensed in *ortho*-positions with a five-ring. In the method of writing *b*, which is commonly employed, it is not so clear that the pyrimidine ring belongs to the diazines. In this book, therefore, method *a* will be used.

Purine $C_5H_4N_4$, a very feebly basic compound, m.p. 217° , which is readily soluble in alcohol and water, cannot be obtained by directly reducing uric acid.

By the action of phosphorus oxychloride on uric acid there is produced *2,6,8-trichloropurine* (I); when this compound is treated at 0° with phosphonium iodide and hydriodic acid, *diiodopurine* (II) is produced, from which purine (III) itself is formed by warming with zinc dust and water:

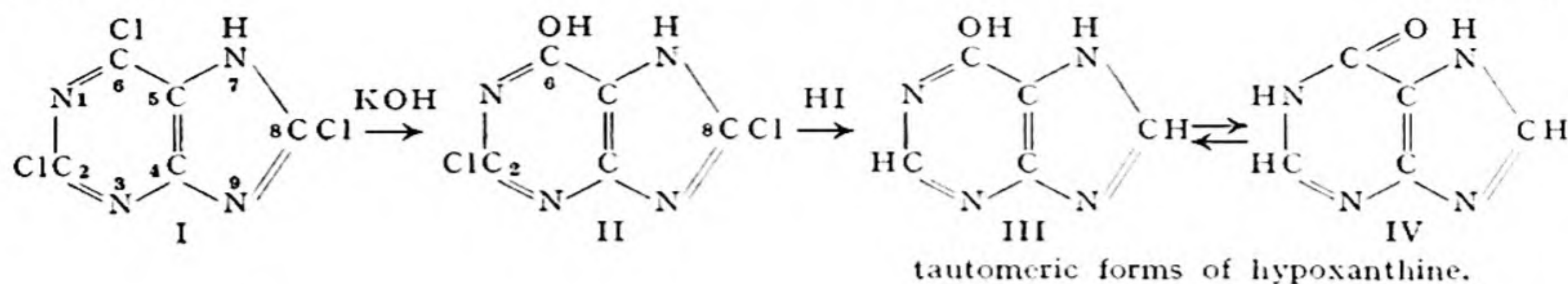


According to this method of formation, structure IV might also be ascribed to purine; however, III is in agreement with the structure of some of its derivatives which have been obtained synthetically.

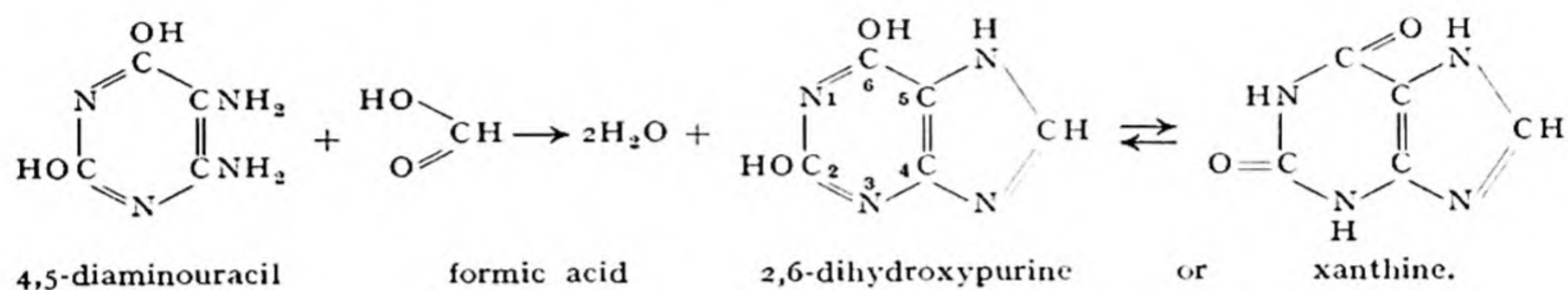
Compounds of the uric acid group may be considered as derivatives of purine so that a rational nomenclature is possible. Uric acid in the enol-form may be called *2,6,8-trihydroxypurine*.

Some of the naturally occurring purine derivatives will now be discussed.

Hypoxanthine or *6-hydroxypurine* $C_5H_4ON_4$, occurs in both the animal and vegetable kingdoms. It may be obtained in the following way from 2,6,8-trichloropurine (I) The chlorine atom in the 6-position is easily replaced by a hydroxyl group by the action of caustic potash at 100° . The resultant 2,8-dichloro-6-hydroxypurine (II) is converted into hypoxanthine (III) by reduction with hydriodic acid:



348. *Xanthine* or *2,6-dihydroxypurine* $C_5H_4O_2N_4$, occurs in many plants and in various animal organs; it occurs also in extremely small amounts in urine. The structure of xanthine follows from the formation of alloxan and urea in its oxidation with hydrochloric acid and potassium chlorate and further, from the TRAUBE synthesis (compare 346):



Xanthine is also formed by warming 2,6,8-trichloropurine with sodium ethylate to produce 2,6-diethoxy-8-chloropurine, which is converted into xanthine by heating with hydriodic acid, the ethyl groups and the chlorine atom being replaced by atoms of hydrogen. Xanthine is very sparingly soluble in water and possesses feebly basic properties.

Theobromine or *3,7-dimethylxanthine* $C_7H_8O_2N_4$, occurs in cocoa beans (the seeds of *theobroma cacao*). The unroasted beans contain 1.5–1.8 % of theobromine. The latter is a colourless, crystalline substance, melting at 351° , which is very sparingly soluble in water and possesses a bitter taste. It is obtained from cocoa pods and can be prepared on a commercial scale from uric acid.

Theobromine is used in medicine as a diuretic; the double salts of the sodium salt of theobromine with sodium salicylate, *Diuretin*, or with sodium lactate, *Theolactin*, are used for the same purpose. These substances are more soluble in water than theobromine.

Caffeine, *theine* or *1,3,7-trimethylxanthine* $C_8H_{10}O_2N_4$, occurs in coffee beans; it was discovered round about 1820, independently by RUNGE, ROBIQUET, PELLETIER and CAVENTOU. Subsequently it was found that caffeine from coffee is identical with theine from tea. Caffeine crystallises from water in glittering, silky needles having the composition $C_8H_{10}O_2N_4 \cdot H_2O$.

The anhydrous substance melts at 236.5° and sublimes at a lower temperature. It is readily soluble in warm water and sparingly soluble in cold.

Unroasted coffee beans, the kernels from the seeds of *coffea arabica*, contain about 1 % of caffeine, the content of china tea (the dried leaves of *thea chinensis*) varies between 1.1 and 4.7 %; cola nuts contain about 1.7 %, paraguayan tea or maté, the dried leaves of *ilex paraguayensis*, contains on the average 0.7 % of caffeine.

Caffeine stimulates the activity of the central nervous system and increases that of the heart. It is used in medicine as such and in the form of double compounds *e.g.* with sodium salicylate. Caffeine can be obtained from tea leaves; it is also prepared by methylating theobromine and can be prepared from uric acid.

Structure of theobromine and caffeine. Theobromine can be obtained by warming the lead salt of xanthine with methyl iodide, whereby two methyl groups are introduced. It is therefore a dimethylxanthine.

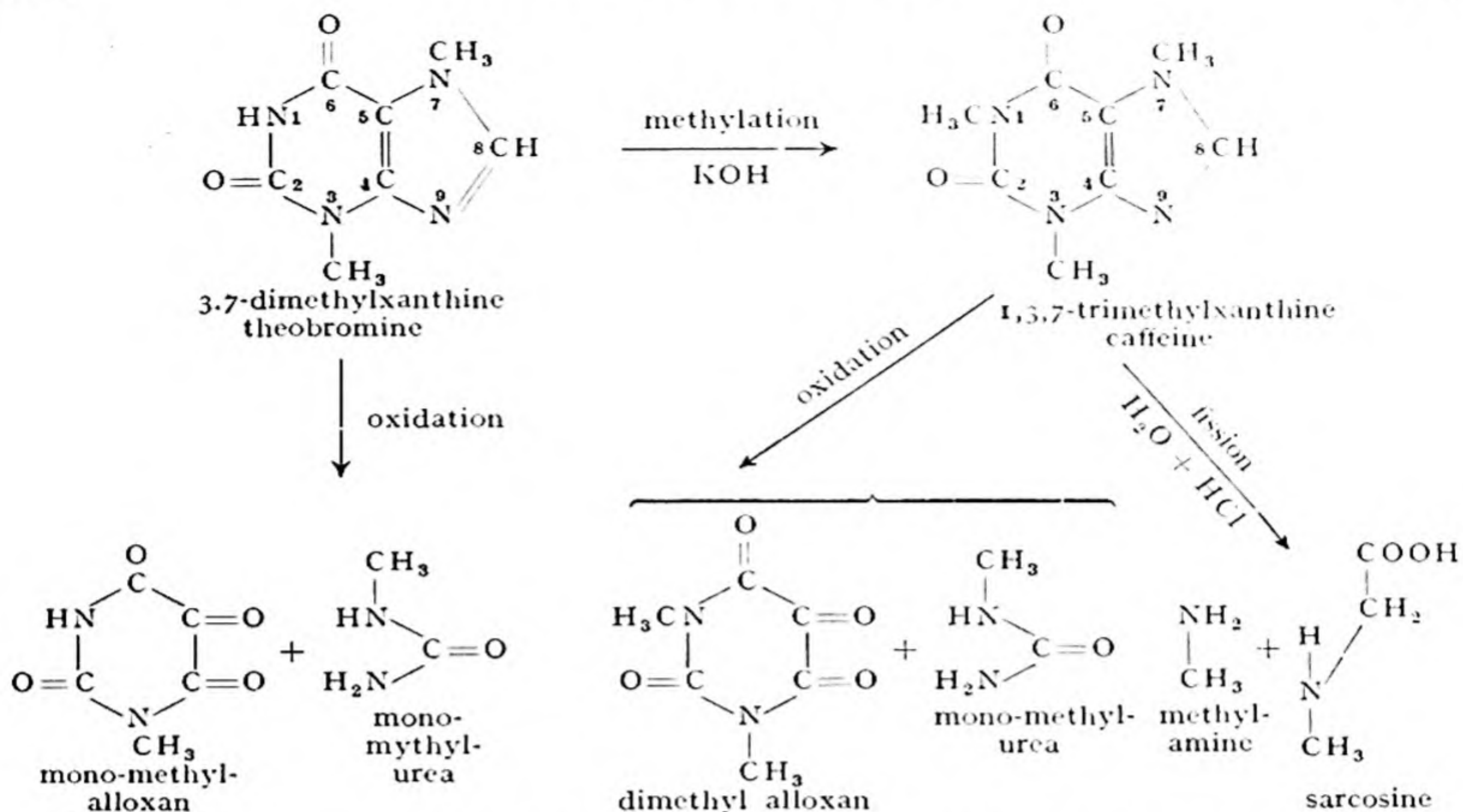
By methylation in alkaline solution, a trimethylxanthine, caffeine, is produced in which the three methyl groups are attached to each of the three nitrogen atoms, for, when caffeine is heated with hydrochloric acid, methylamine and sarcosine (195) $\text{CH}_3\text{NHCH}_2\text{COOH}$, are formed in quantities agreeing with three $>\text{NCH}_3$ groups in the molecule.

Dimethylalloxan and monomethylurea are produced by oxidising caffeine with potassium chlorate and hydrochloric acid. Hence two of the methyl groups in the caffeine molecule are substituted in the pyrimidine nucleus in positions 1 and 3, since the methyl groups are attached to nitrogen. The third methyl group is situated in the iminazole-ring, for this methyl group also is attached to a nitrogen atom and therefore in position 7. From the formula of purine, nitrogen atom 9 carries no hydrogen atom and therefore no substituent can be attached to this atom. Position 7 for the third methyl group in caffeine is confirmed by synthesis and at the same time it affords a proof for the correctness of the purine formula. Further details, however, cannot be gone into here.

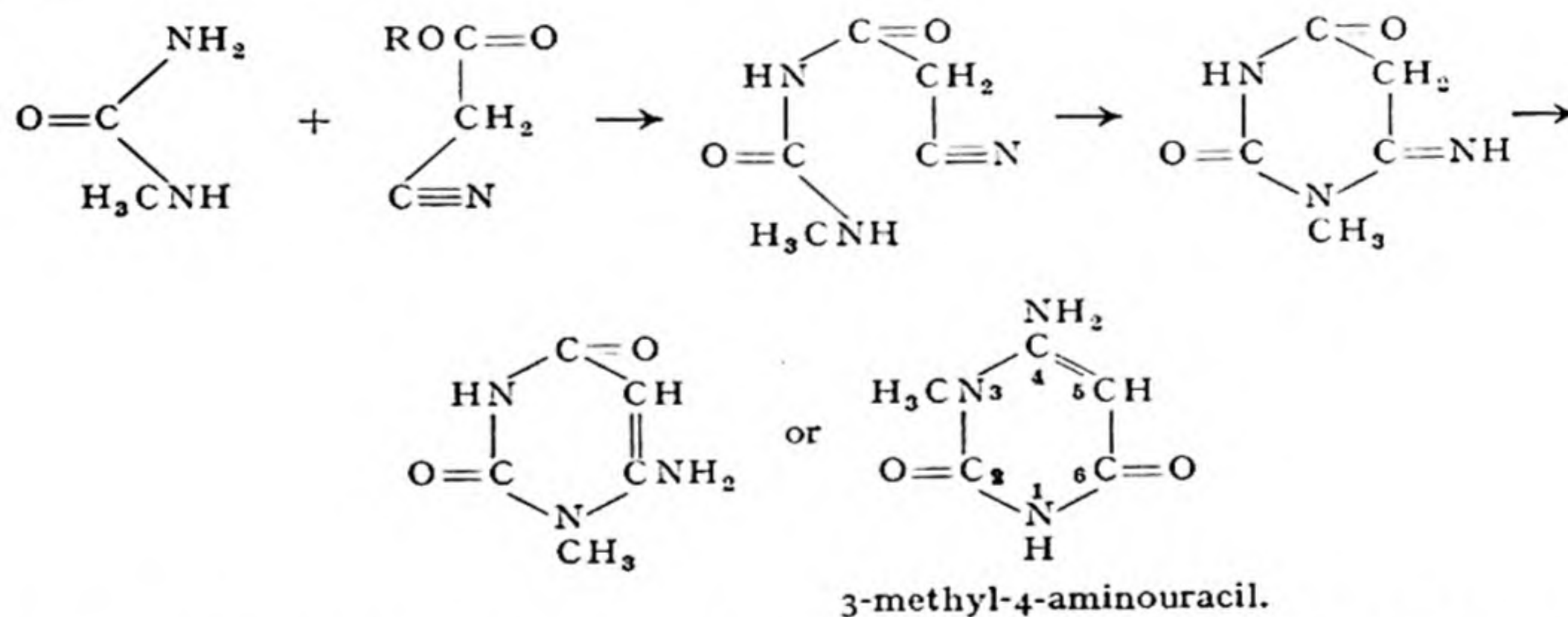
By oxidising theobromine with chlorine in presence of water, *mono-methylalloxan* and *mono-methylurea* are formed (see formula on page 589).

One of the two methyl groups in theobromine must therefore be attached to position 7 and the other to position 1 or 3.

The following synthesis proves that position 3 is occupied by a methyl group.



Theobromine is prepared by a Traube synthesis in which 4-amino-3-methyluracil is obtained from mono-methylurea, and is then converted into 3-methylxanthine by the method described on page 587; the latter compound is then methylated to give theobromine:

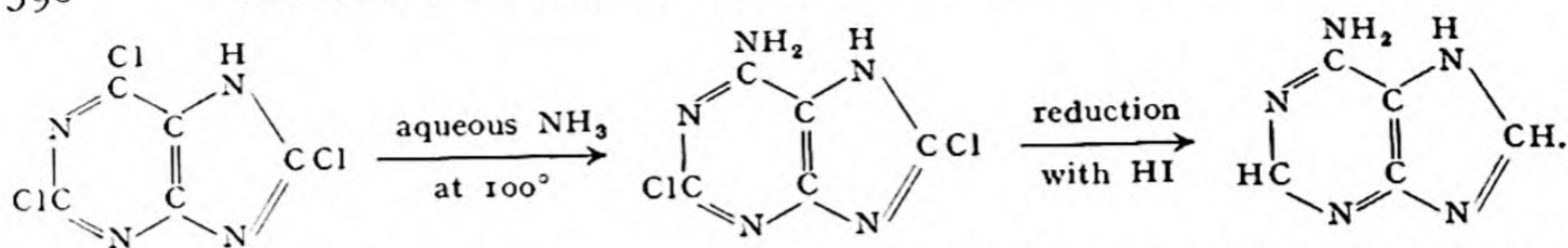


Theophylline or *1,3-dimethylxanthine* $C_7H_8O_2N_4$, is an isomer of theobromine. It melts at 268° and is sparingly soluble in cold but readily soluble in warm water. The solution reacts neutral. This compound occurs in small amounts in tea leaves but it is difficult to isolate it from this source. It can be prepared from uric acid or by a Traube synthesis. Theophylline has a powerful diuretic action and is used in medicine.

Adenine or *6-aminopurine* $C_5H_5N_2$ is sparingly soluble in water from which it crystallises with three molecules of water of crystallisation; the solution is neutral in reaction. It forms salts with inorganic acids and also dissolves in strong bases.

Adenine occurs very widely distributed in small quantities throughout the vegetable and animal kingdoms, especially as a fission product of nucleic acids (349).

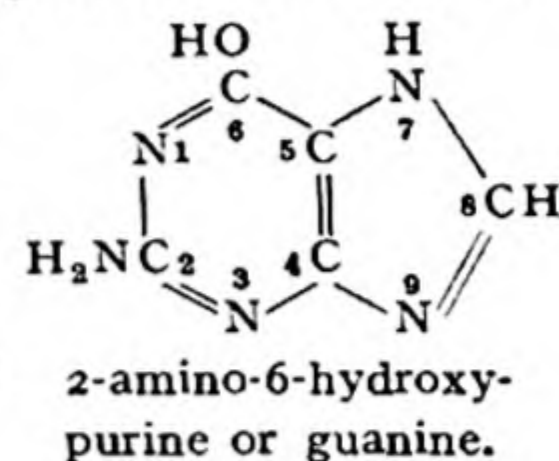
It is obtained in the following way from trichloropurine (E. FISCHER):



The structure of adenine is in accordance with the formation of hypoxanthine by the action of nitrous acid on adenine.

Guanine or *2-amino-6-hydroxypurine* $\text{C}_5\text{H}_5\text{ON}_5$, is very sparingly soluble in water and alcohol. It occurs in plants and animals and is, for example, a constituent of human faeces and of guano. It is converted into xanthine by the action of nitrous acid. Guanidine $\text{H}_2\text{N}(\text{C}=\text{NH})\text{NH}_2$ (153) is produced along with other substances when guanine is oxidised with potassium chlorate and hydrochloric acid.

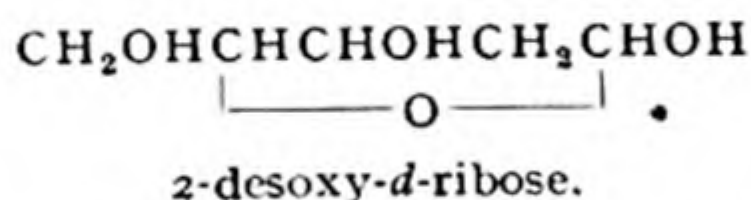
Hence in guanine, one carbon atom must be attached to three nitrogen atoms. From these data the structure of guanine must be as shown annexed.



Nucleosides, mononucleotides and polynucleotides or nucleic acids

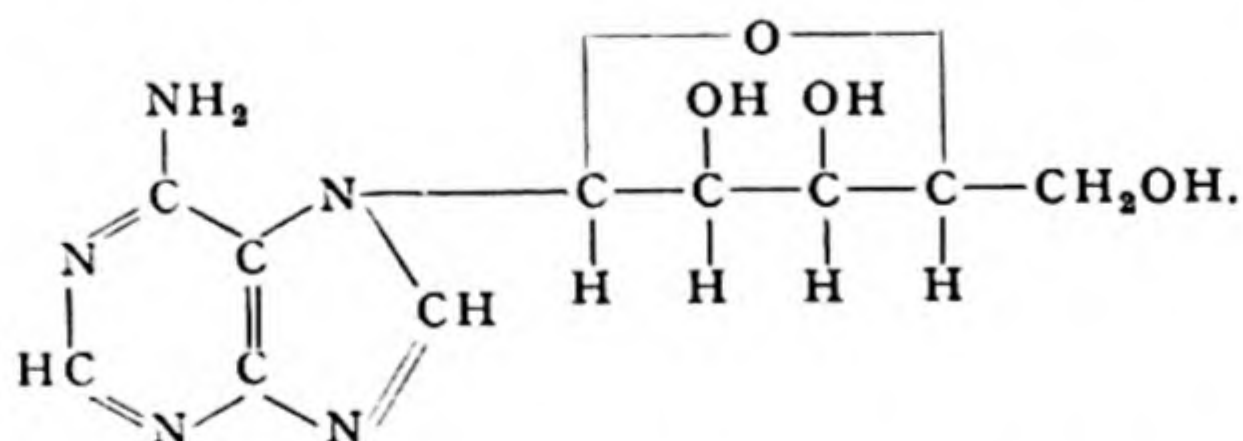
349. *Nucleosides* are composed of a mono-saccharide residue (159) and a pyrimidine (344) or a purine derivative (346) combined in the form of a glucoside (179).

d-Ribose, 2-desoxy-*d*-ribose and *d*-glucose have been found as mono-saccharide components. *Desoxy-sugars* are derivatives of mono-saccharides in which a $>\text{CHOH}$ -group is replaced by a $>\text{CH}_2$ group, thus:

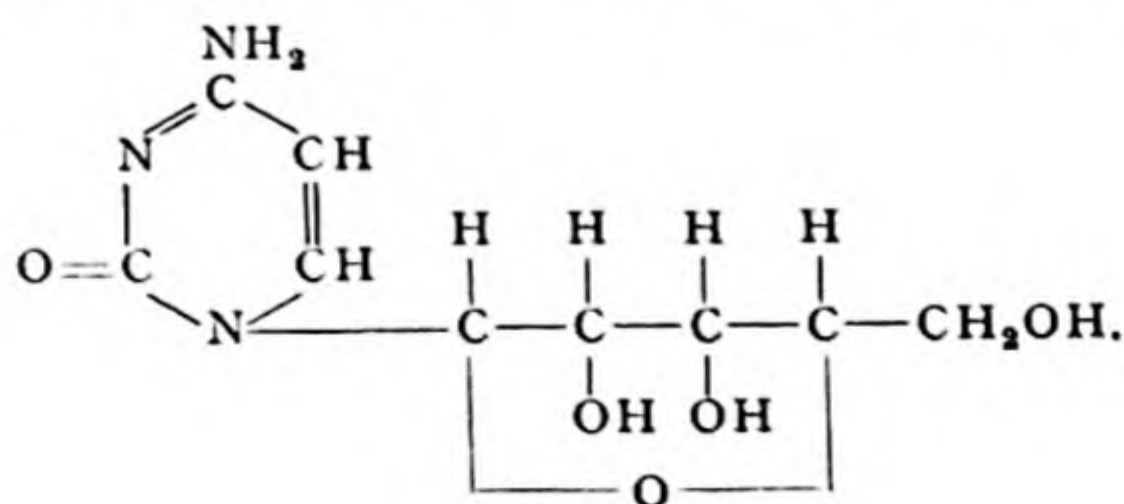


Adenine and guanine are found as purine derivatives and cytosine, uracil, thymine and methylcytosine (344) as pyrimidine derivatives.

Adenosine, i.e. adeny-7-*d*-ribofuranoside is an example of a purine-nucleoside:



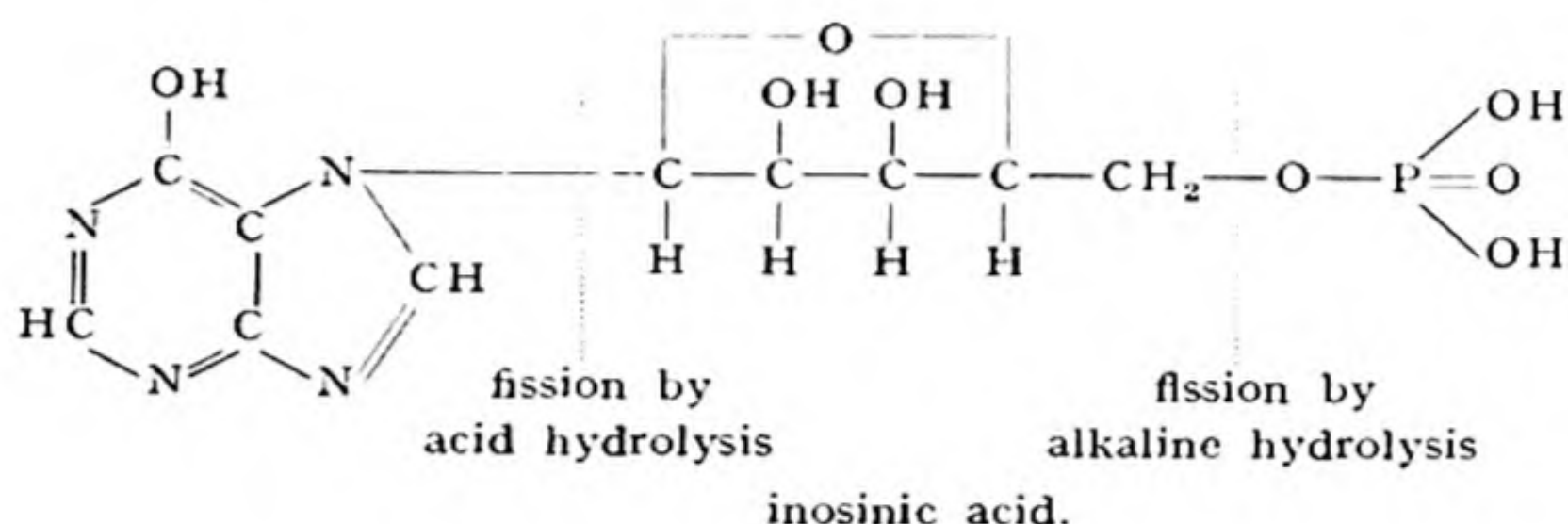
Cytidine or cytosyl-*d*-ribofuranoside is a pyrimidine nucleoside:



Both these nucleosides are found as fission products or nucleic acids. The nucleosides are crystalline substances, which are soluble in water but insoluble in most organic solvents. The purine-nucleosides are split up by very dilute mineral acids into *d*-ribose and a purine derivative; the pyrimidine-nucleosides are only split up by more concentrated solutions of mineral acids, which bring about the decomposition of the monosaccharide component.

Mononucleotides are phosphate esters of nucleosides; various nucleotides are found in animal and vegetable tissues; as an example *inosinic acid*, which occurs in meat extract, may be mentioned.

By acid hydrolysis it is split up into a phosphate ester of ribose and by alkaline hydrolysis *inosine* or *hypoxanthine-riboside* is produced:



Adenylic acid is similarly constituted to inosinic acid; it occurs in muscle and contains adenine as a structural unit.

Diphosphate esters also occur in the nucleotides as well as monophosphate esters.

Nucleic acids or *polynucleotides* are compounds of high molecular weight which give nucleotides and nucleosides by hydrolytic fission.

Compounds derived from nucleic acids with proteins, histones or protamines are the chief constituents of the nuclei of vegetable and animal cells.

To this class of compounds belong the nucleoproteins (201).

One nucleic acid from yeast gives on hydrolysis, four mono-nucleotides, viz. *guanine-ribosephosphoric acid*, *uracil-ribosephosphoric acid*, *cytosineribose-phosphoric acid* and *adenineribose-phosphoric acid* which are probably combined in the molecule in the form of esters. (P. A. LEVENE).

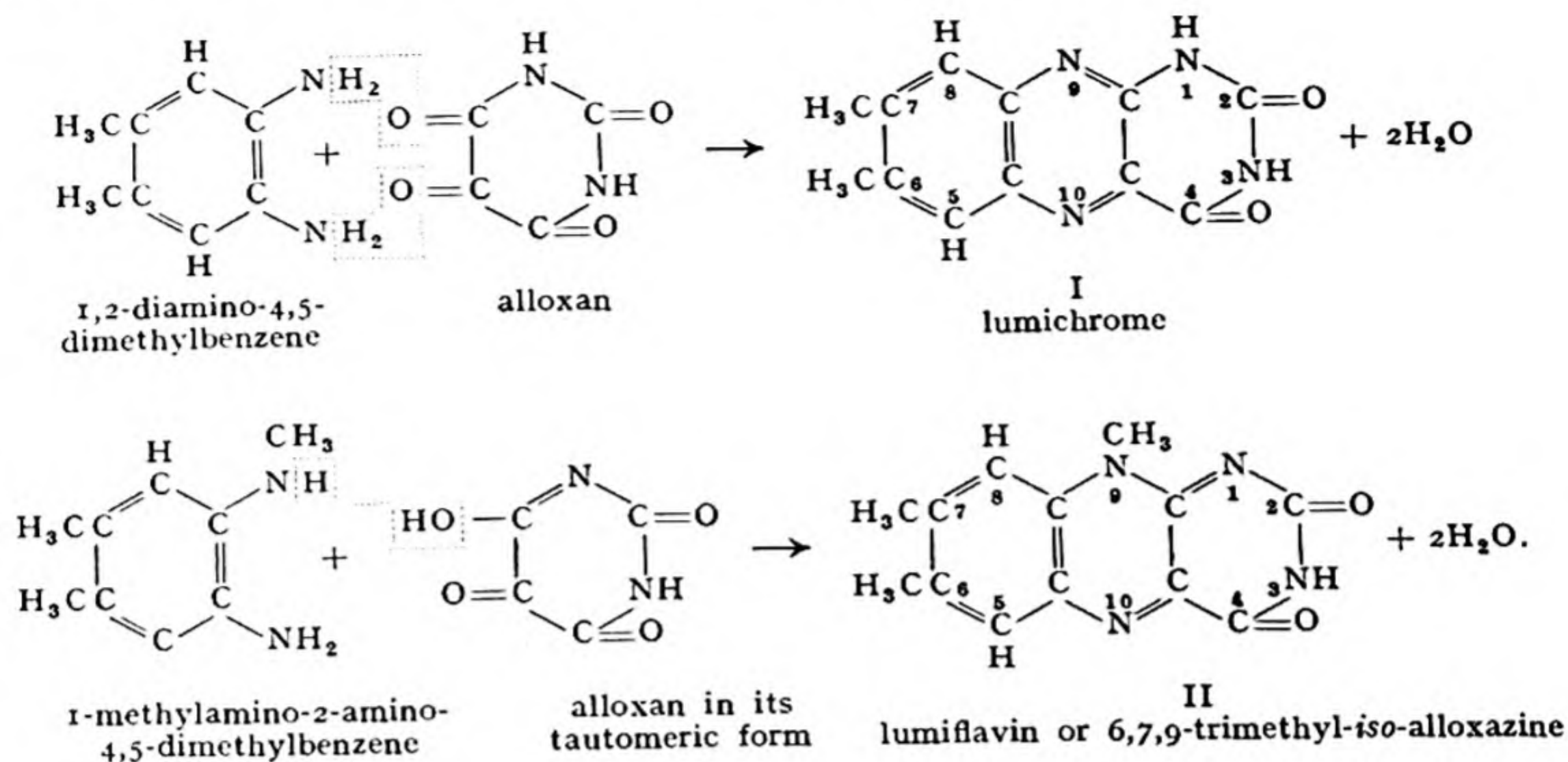
Lactoflavin (riboflavin) or Vitamin-B₂

350. *Vitamin-B₂* C₁₇H₂₀O₆N₄ (see 306), which has been given the name of *lactoflavin* because of its yellow colour and its presence in milk, melts at 280–282° and the aqueous solution shows a yellow-green fluorescence. The structure of lactoflavin has been established by R. KUHN and P. KARRER.

By the action of sunlight on a methyl alcoholic solution of lactoflavin, the latter substance is decomposed and a yellow coloured substance, *lumichrome* C₁₂H₁₀O₂N₄ (I) is produced.

By irradiating a weakly alkaline aqueous solution of lactoflavin, another dyestuff, *lumiflavin* C₁₃H₁₂O₂N₄ (II) is formed. Compounds I and II show similar properties to *alloxazine*, which had long been known and which is produced by condensation of

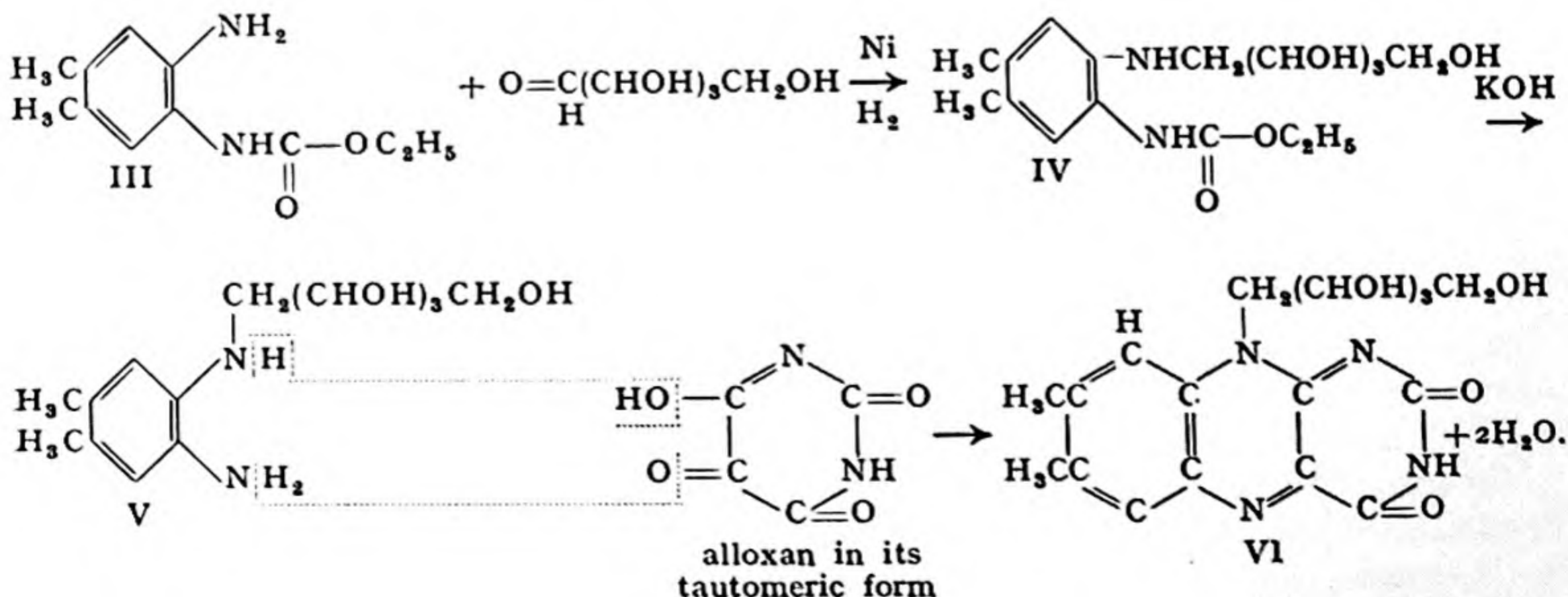
alloxan (346) with 1,2-diaminobenzene in acid solution. The structure of lumichrome and of lumiflavin follows from the methods of synthesis:



Compounds I and II contain the ring-system of a pyrazine-ring (342) condensed with a benzene-ring and also with a pyrimidine-ring (344).

When the composition of lactoflavin is compared with that of lumiflavin, it is seen that the latter contains a C₄H₈O₄-group less than the former. Lactoflavin contains four hydroxyl groups as is shown by acetylation. From this it follows that lactoflavin may be a derivative of lumiflavin in which the CH₂-group attached to position 9 is replaced by CH₂OH(CHOH)₃CH₂—. A number of such isomeric compounds were prepared by synthesis and the *d*-ribityl-derivative appeared to be identical with naturally occurring riboflavin. The synthesis is carried out as follows:

An equimolecular mixture of 1-amino-2-carbethoxyamino-4,5-dimethylbenzene (III) and *d*-ribose is treated with hydrogen in the presence of finely divided nickel to produce 2-carbethoxyamino-4,5-dimethylphenylribitylamine (IV). It must be concluded that the —CHO group in ribose reacts with the free amino-group in III with the elimination of water and the compound so obtained then takes up two atoms of hydrogen:

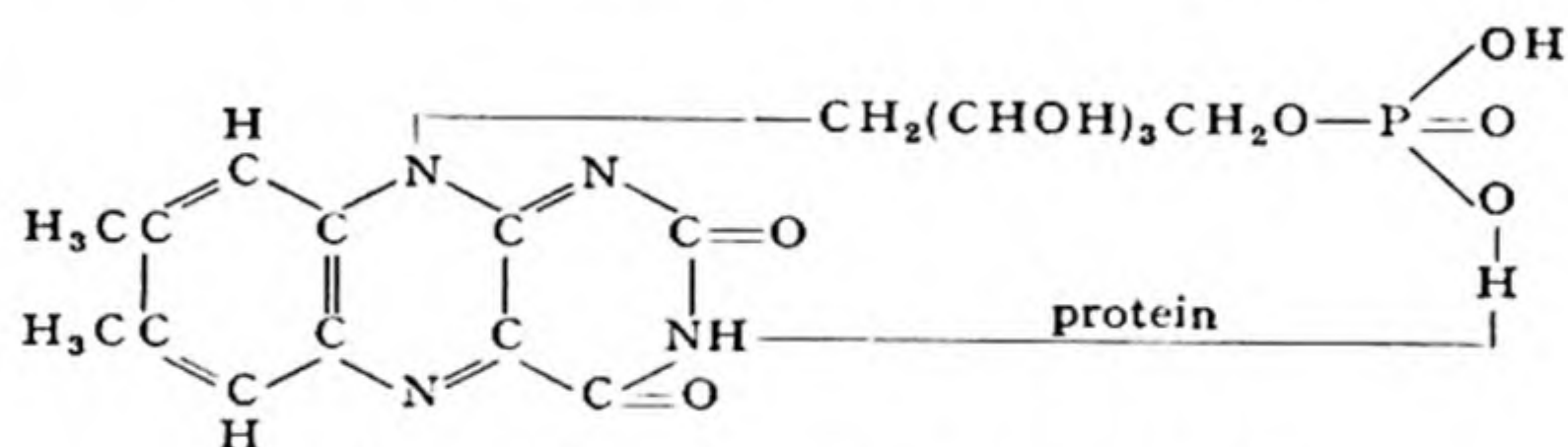


Alkaline hydrolysis of IV gives 2-amino-4,5-dimethylphenylribitylamine (V). When this base is warmed in acid solution with alloxan, 6,7-dimethyl-9-ribitylisoalloxazine or riboflavin (VI) is produced.

In a similar way a number of isomers of lactoflavin have been prepared in which the *l*-ribityl or *d*- or *l*-arabityl or *d*-xylityl group is introduced in place of the *d*-ribityl group. These compounds either fail to show the growth promoting activity of vitamin-B₂ altogether or show it only to a very much lesser degree. This activity is present in homologues of lactoflavin containing only one methyl group. Hence the *d*-ribityl group is necessary for the promotion of growth.

Hydrogen-transferring enzymes

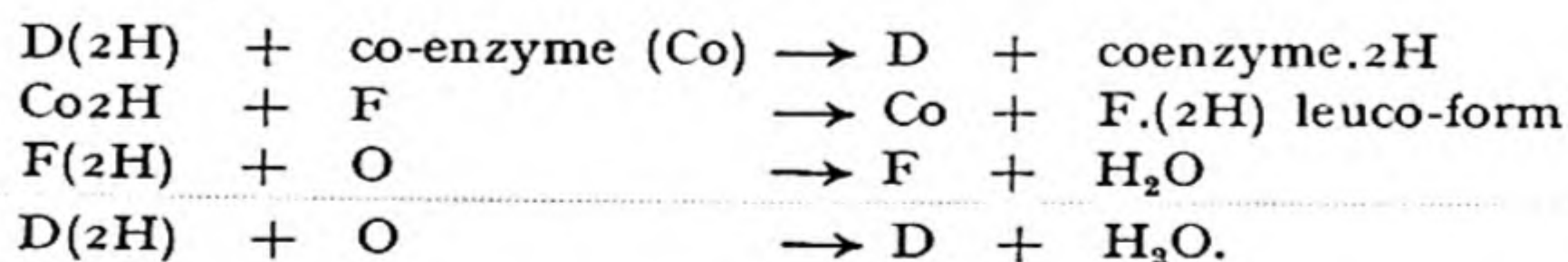
351. The yellow respiratory enzyme, a holo-ferment (208) occurring in many living cells and isolated, for example, from yeast, fulfils a function in the oxidation processes in the living cell. According to researches by WARBURG, KUHN, THEORELL and their co-workers, this holo-enzyme consists of a *co-enzyme* and an *apo-enzyme*, the latter being a protein. The co-enzyme is a phosphoric acid ester of riboflavin and has been synthesised. The phosphoric acid is probably esterified with the terminal group in the ribityl residue. It is assumed that the protein, as an amphoteric substance, is combined through a basic group with one of the hydroxyl groups in the phosphoric acid, while an acid grouping in the protein is combined with the NH-group in the pyrimidine ring:



yellow respiratory enzyme of WARBURG.

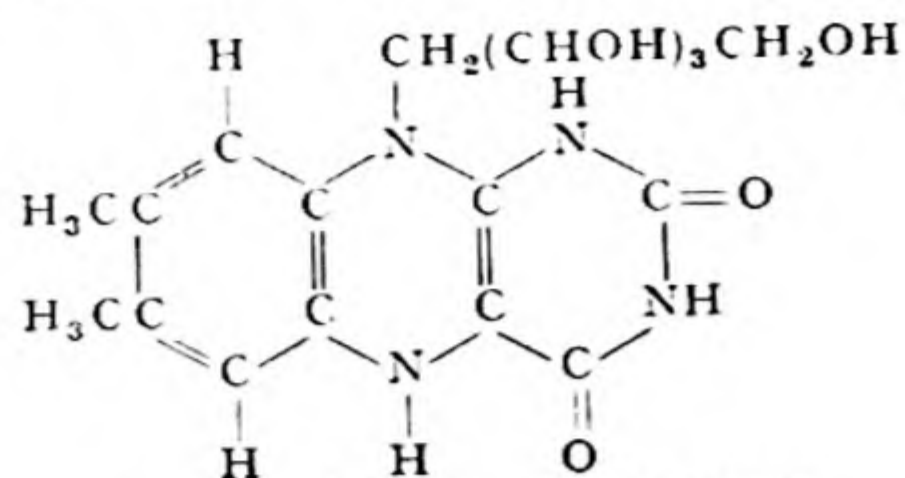
The yellow respiratory ferment can be readily reduced to a leuco-compound. This reduction takes place in the living cell by means of a hydrogen-transferring co-enzyme (WARBURG), which has the power of taking up hydrogen from a substance which will give up hydrogen [hydrogen donator D(2H)] and transferring this hydrogen to the yellow ferment F, thereby reducing it to a leuco-compound F(2H). This leuco-compound is then oxidised by atmospheric oxygen either directly or through the agency of another enzyme-system (cytochrome).

Schematically the process is represented as follows:



The result is that two atoms of hydrogen are split off as water from the substance D(2H), which cannot be oxidised by atmospheric oxygen directly.

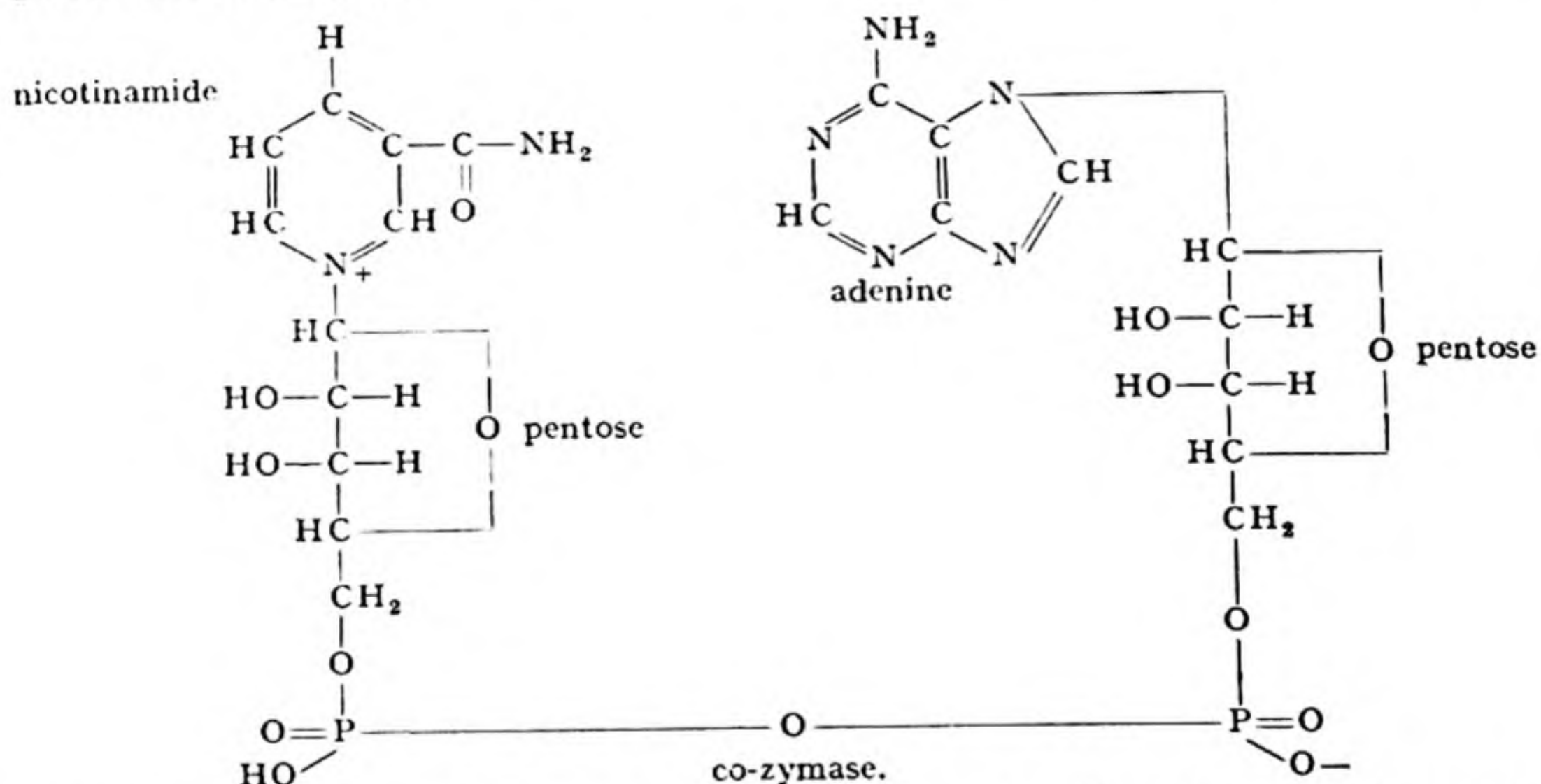
Now it is assumed, that in the leuco-form of the yellow respiratory enzyme, the two atoms of hydrogen are taken up in the iso-alloxazine ring, which becomes converted into a partially hydrogenated ring:



leuco-derivative of lactoflavin.

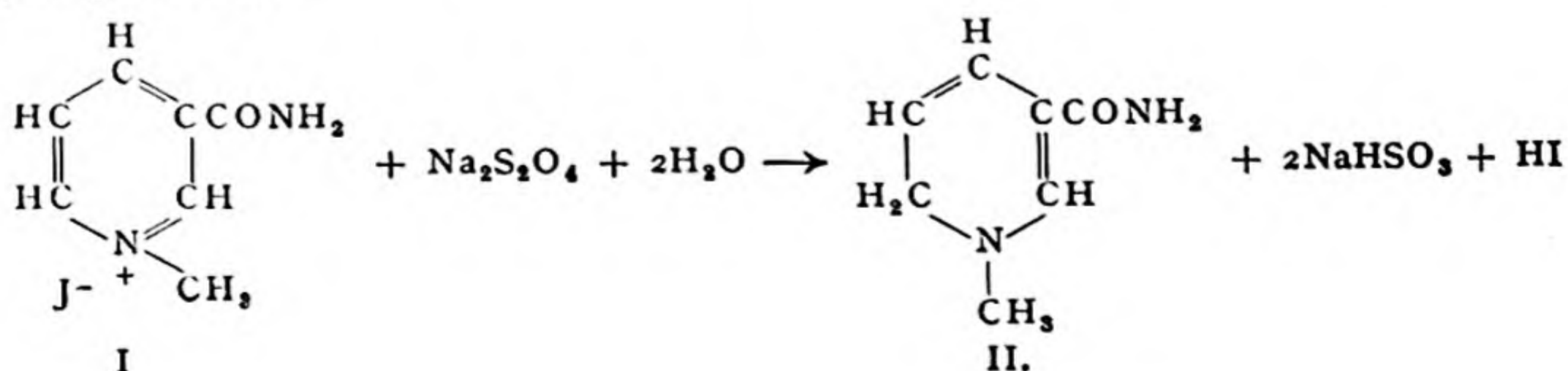
WARBURG's *hydrogen-transferring co-ferment*. In chemical structure this co-ferment is closely related to co-enzyme, one of the enzymes of the zymase-complex, which can also bring about the transference of hydrogen (see 193). From the researches of VON EULER and WARBURG, both enzymes are to be considered as nucleotides (349).

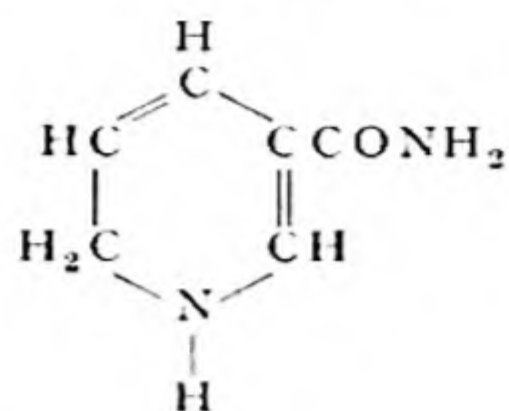
Co-enzyme has a molecular weight of about 700. On hydrolytic fission it is broken down into two molecules of phosphoric acid, a molecule of adenine (348), a molecule of nicotinamide (335) and a pentose. According to VON EULER, co-enzyme must be represented as follows:



The nitrogen atom in the pyridine group carries a positive charge and is combined in the form of an internal salt with a negatively charged oxygen atom of a phosphoric acid residue.

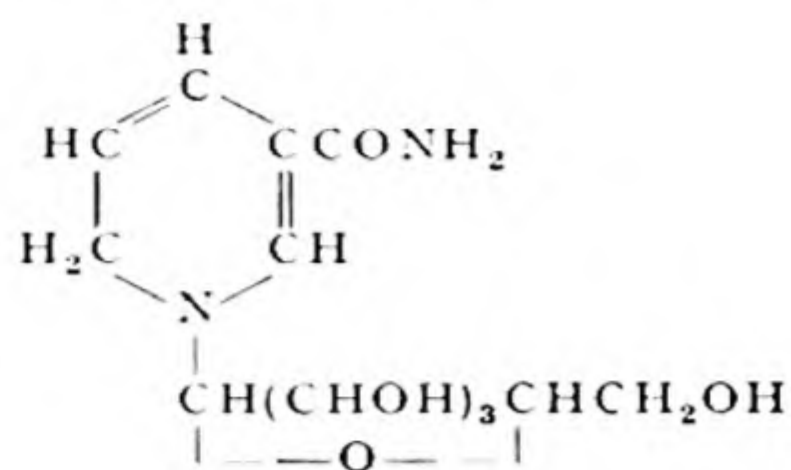
The active group in the co-enzyme molecule, which can take up and part with two atoms of hydrogen, is the nicotinamide grouping. It has been found that quaternary salts of this compound, I, can be reduced in aqueous solution by sodium hydrosulphite $\text{Na}_2\text{S}_2\text{O}_4$, whereby a methylated derivative II of 1,6-dihydropyridine 3-carbonamide (III) is produced:





III

1,6-dihydropyridine-
3-carbonamide (unknown)



IV.

Compound II, which can be isolated in a practically pure state, is very easily oxidised. The ultra-violet spectrum of II is quite different from that of I.

KARRER has prepared a compound having the structure IV; this is the N-glucosido-derivative of 1,2-dihydropyridine 5-carbonamide. He has also prepared derivatives in which there is a pentose residue instead of a glucose residue.

In alkaline solutions, these compounds show an absorption maximum in the ultra-violet at 3400 Å. On acidification, this maximum disappears and a maximum appears at 2250 Å. This absorption spectrum agrees exactly with the absorption spectrum produced when WARBURG's hydrogen-transferring enzyme or co-enzyme is reduced with sodium hydrosulphite. From this description it is very probable therefore, that the nicotinamide group in which the nuclear nitrogen atom is quaternised, is the active group in co-enzyme and the co-ferment of WARBURG. The latter has a molecular weight of about 800 and on hydrolysis gives a pentose, 1 mol. of adenine, 1 mol. of nicotinamide and 3 mols. of phosphoric acid.

CHAPTER 15

ALKALOIDS

352. The name alkaloids, for the nitrogenous basic compounds occurring in plants, is connected with the discovery of the first representative of this group of compounds, *morphine*, which was isolated by SERTÜRNER in 1814 from opium. This investigator found that morphine gives salts with acids and therefore must be considered as a base. This was the first example of a basic, nitrogenous carbon compound, therefore it was given the name alkaloid, *i.e.* an alkali-like compound. The composition of morphine $C_{17}H_{19}O_3N$ was determined in 1831 by LIEBIG.

In 1820 PELLETIER and CAVENTOU discovered two other alkaloids, which they isolated from cinchona bark, namely, *quinine*, $C_{20}H_{24}O_2N_2$ and *cinchonine* $C_{19}H_{22}ON_2$. In 1828, POSSELT and REIMANN isolated a liquid with basic properties from tobacco, namely, *nicotine* $C_{10}H_{14}N_2$. Thus by the term alkaloid was understood a nitrogenous basic compound of complicated composition, which occurs in the vegetable kingdom.

Not until 1848 did WURTZ discover the simplest organic nitrogenous bases, the aliphatic amines, some of which, like methylamine and trimethylamine, also occur in the vegetable kingdom; these compounds are not, however, included in the alkaloids.

As more alkaloids were examined, it became apparent, that as regards their structures, these vegetable bases belonged to very diverse groups.

These compounds are treated in a separate chapter for historical reasons. The vegetable bases of the purine group, which are frequently looked upon as alkaloids, have already been discussed in 347.

Amino-acids with basic characteristics are not included in the alkaloids; on the other hand, some amines, which can be obtained by simple reactions from amino-acids, like histamine (199, 325) and tyramine (239), do belong to this group.

Many alkaloids contain heterocyclic ring-systems with nitrogen atoms combined in the ring; they are divided into groups depending on the nature of the ring-system. At present, a few hundred alkaloids are known, including a number of unknown or only partially known constitutions. The structures of the majority have been elucidated only after difficult and tedious investigations.

Plants which contain alkaloids, belong chiefly to the dicotyledons, although some alkaloid-bearing plants occur among the mono-cotyledons and even amongst the cryptogams and the gymnosperms. Amongst the dicotyledons there are some families which are very rich in plants bearing alkaloids, *e.g.* the papaveracea, papillionaceae, ranunculaceae, rubiaceae, etc. A plant species containing alkaloids very seldom contains just one alkaloid but usually contains various bases closely related in structure.

Alkaloids occur in plants combined with acids like oxalic acid, acetic acid, lactic acid, malic acid, tartaric acid and citric acid in the form of salts.

In order to isolate alkaloids from plants, the vegetable material is finely divided and extracted with acidulated water, when the alkaloids and other substances such as saccharides, colouring matters, etc., pass into solution. The aqueous extract is then basified and the liberated alkaloids are recovered by extraction with solvents like ether or chloroform, or in the case of volatile alkaloids, by steam distillation. For purifying the alkaloids, the free bases are again converted into salts which are purified by recrystallisation.

Many alkaloids can be precipitated from aqueous solution by tannic acid, phosphotungstic acid, phosphomolybdic acid, picric acid, platinum chloride, mercury salts or iodine-potassium iodide.

The alkaloids are usually identified by microscopical examination of the crystalline form of the free bases or their salts, by the ultra-violet absorption spectrum and by the optical rotation. Sometimes they are recognised by their pharmacological properties.

Colour reactions are known for some alkaloids but they are seldom so specific that they are in themselves sufficient to identify a particular alkaloid with certainty. Many alkaloids are extremely poisonous; some show a particular pharmacological action and are therefore of great importance in medicine.

Derivatives of aromatic amines with an amino-group in the side-chain

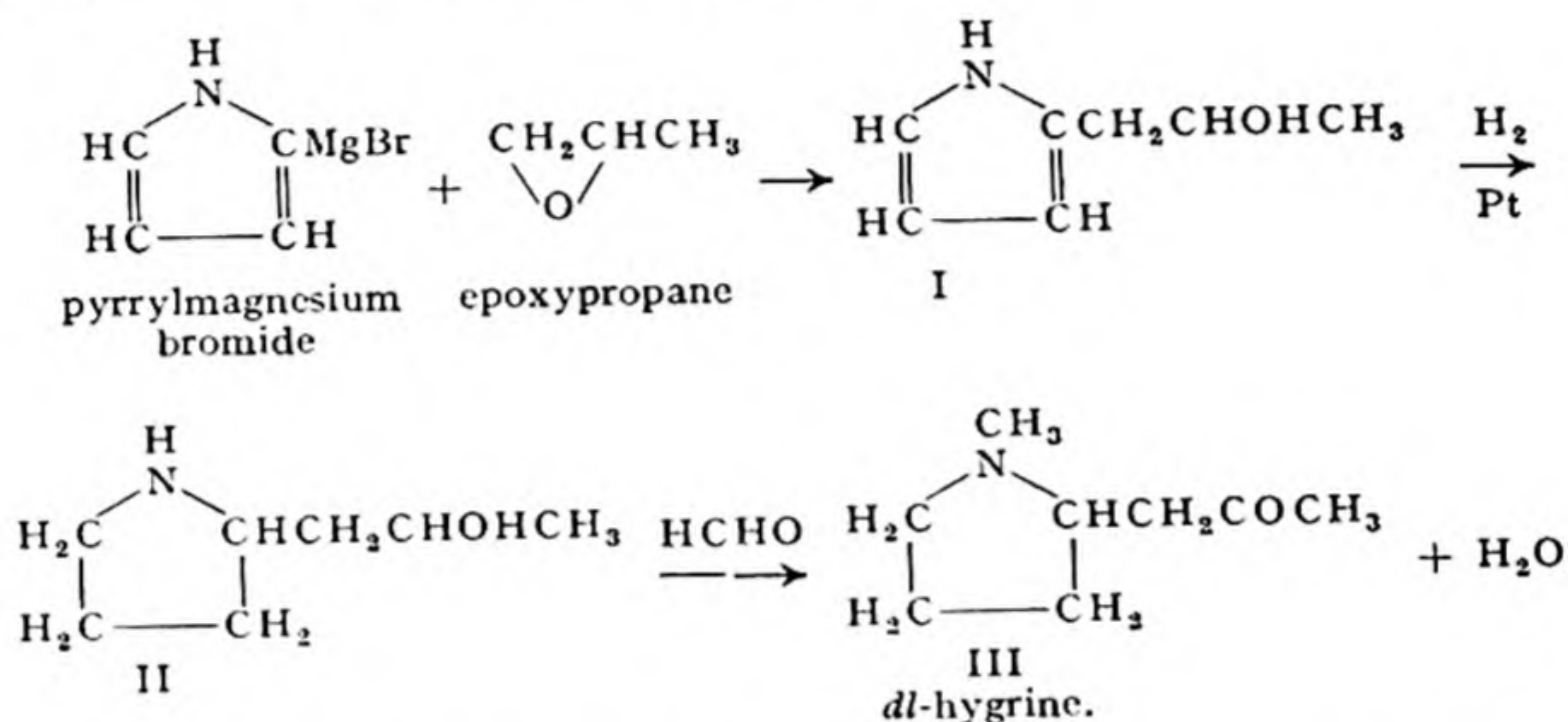
353. *Capsaicine* $C_{18}H_{27}O_3N$, the active constituent in species of capsicum such as *Spanish pepper* and *paprika*, is a derivative of benzylamine, namely, the vanillylamide of a nonene carboxylic acid (*decelenic acid*) $C_9H_{17}COOH$. The structure has been established by synthesis:



For other alkaloids in this group see **239**.

Derivatives of pyrrolidine

354. Hygrine $C_8H_{15}ON$, occurs in Peruvian coca leaves, in which it was discovered in 1862 by WÖHLER and LOSSER. It is a colourless liquid with basic properties, which boils at $193-195^\circ$ and is laevo-rotatory $[\alpha]_D = -1.3^\circ$. It forms an oxime due to the presence of a ketonic group. On oxidation with chromic acid it gives hygric acid (**356**), which loses carbon dioxide on heating and is converted into N-methylpyrrolidine (**314**). From this it follows that hygrine is a derivative of this compound in which there is also a side-chain of three carbon atoms. The structure of the side-chain follows from the following synthesis of *dl*-hygrine (K. HESS):



The last step in this synthesis is rather remarkable. When II is heated with formaldehyde, the secondary alcohol group is oxidised to a ketone group while the NH-group is methylated to give III.

Derivatives of pyridine and piperidine

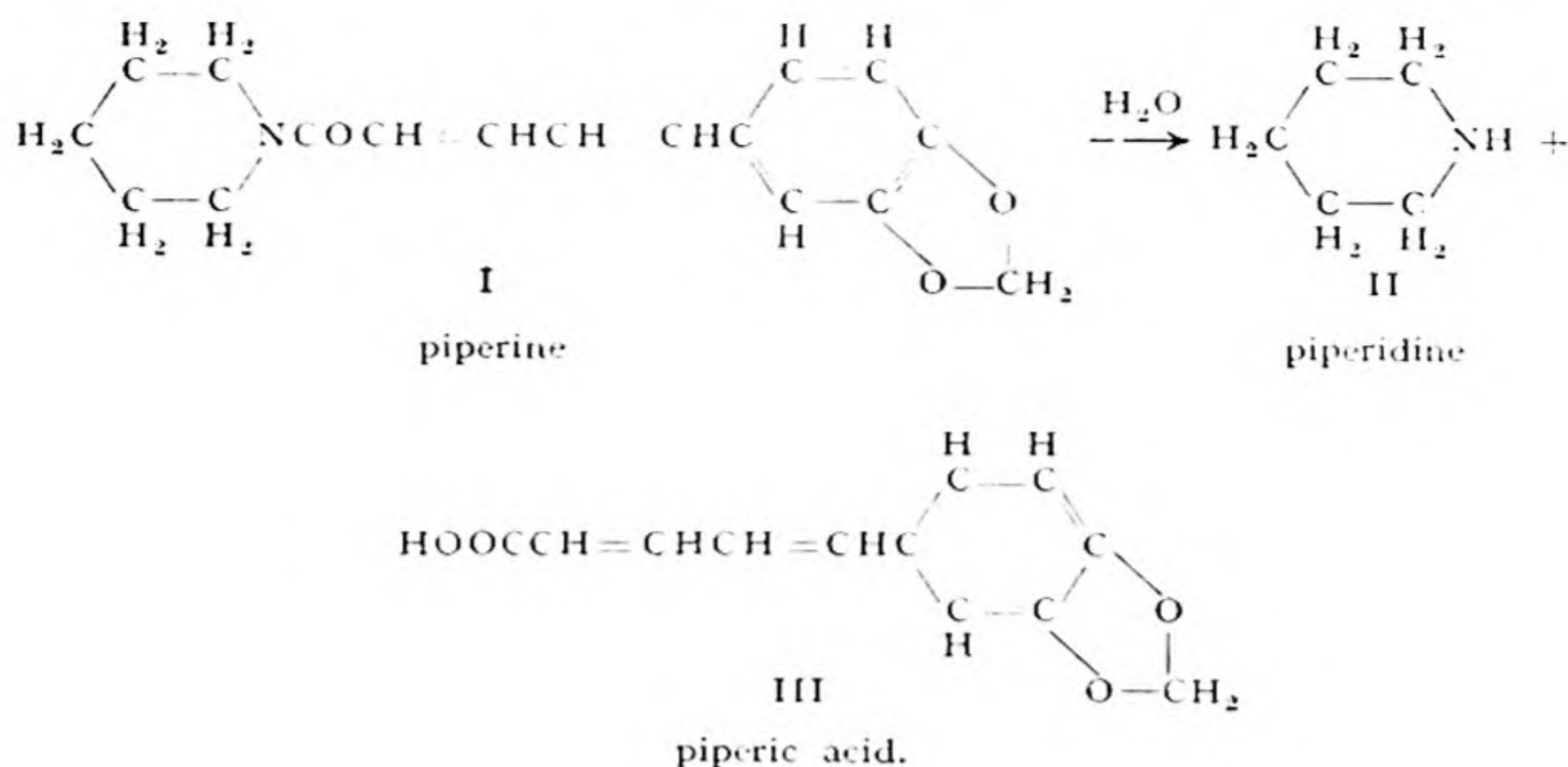
355. Conium alkaloids. The leaves and the fruit of the hemlock (*conium maculatum*) contain a number of closely related alkaloids including *coniine*, *N*-methylconiine $C_9H_{19}N$ and *conhydrine* $C_8H_{17}ON$.

Coniine $C_8H_{17}N$, a liquid with b.p. 166° , $[\alpha]_D^{19} = +15.7$, is sparingly soluble in water but readily soluble in alcohol. The base has a toxic action and causes paralysis of the nerve endings and muscles. The structure of coniine has already been discussed in **334**.

Piperine. The fruits of various kinds of pepper, *e.g.* *piper nigrum*, *piper longum*, contain piperine $C_{17}H_{19}O_3N$, which was isolated from pepper by OERSTEDT in 1819. It is a well defined, crystalline compound, sparingly soluble in water, with a m.p. of 129° ; it is neutral to litmus and has the sharp taste of pepper.

Structure of piperine. Piperine (I) gives piperidine (II) and piperic acid

(III) (269) on hydrolysis. Piperine is therefore a substituted amide of piperic acid:



Alkaloids with two heterocyclic rings

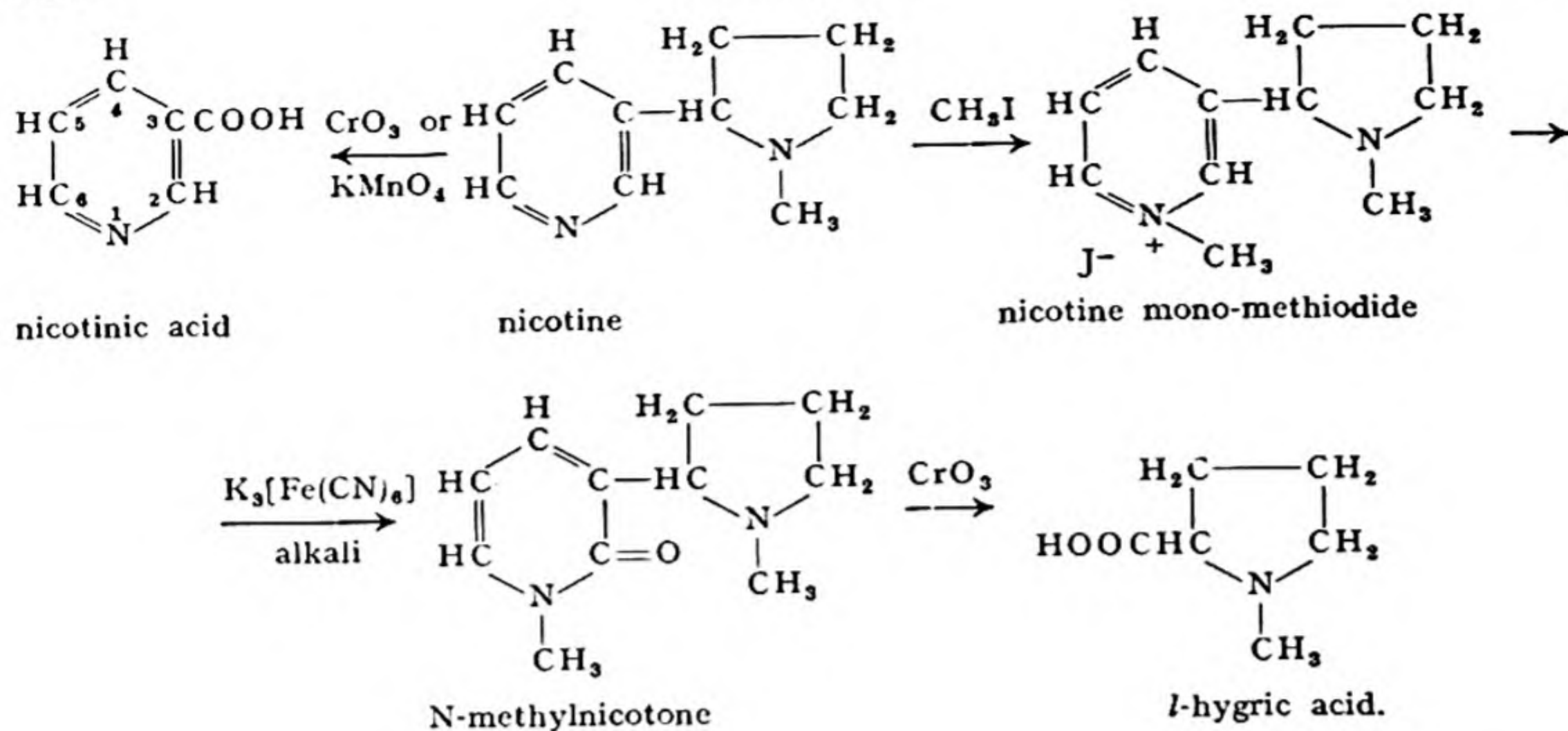
356. Alkaloids from tobacco. A number of alkaloids of closely related structure occur in the leaves of *nicotiana tabacum* and other kinds of *nicotiana*. *Nicotine* $\text{C}_{10}\text{H}_{14}\text{N}_2$ occurs in the greatest amount.

Nicotine occurs in the tobacco plant combined with malic and citric acid; the following also occur in commercial brands of tobacco, *nornicotine* $\text{C}_9\text{H}_{12}\text{N}_2$, *nicotyrine* $\text{C}_{10}\text{H}_{10}\text{N}_2$, *anabasine* $\text{C}_{10}\text{H}_{11}\text{N}_2$ and bases of simpler structure like pyrrolidine (314), N-methylpyrrolidine and piperidine (332).

Nicotine is a colourless liquid, b.p. 247° , $[\alpha]_D = -168.4$, which is miscible in all proportions with water below 60° . It has a tobacco-like smell, which is much less intense from a freshly distilled specimen than from an old preparation; *l*-nicotine is very poisonous; in very small quantities it acts initially as a stimulant to the central and peripheral nervous system, increases the secretion of the salivary glands, contracts the blood vessels and increases the blood pressure.

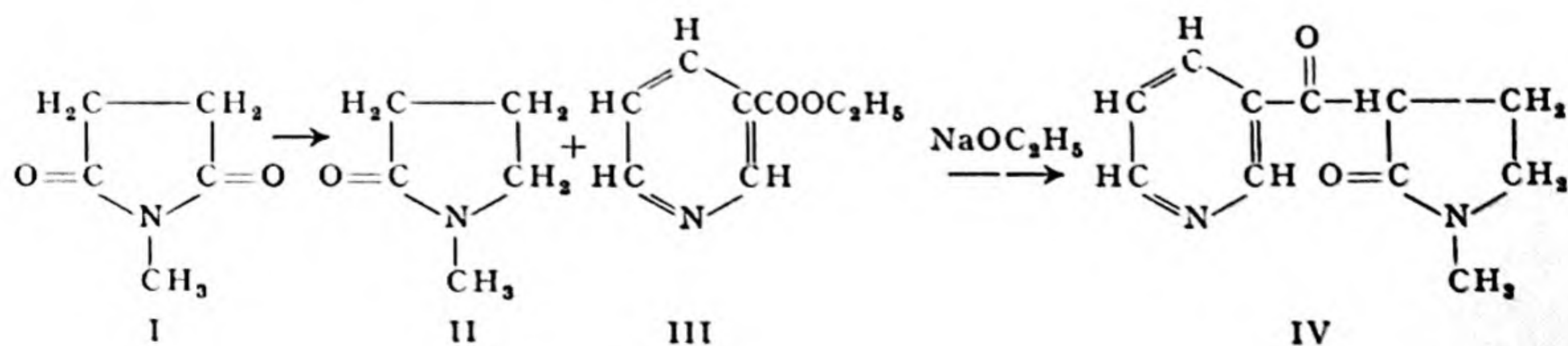
Structure of nicotine. The formula for nicotine, which was suggested by PINNER, explains the following degradation reactions.

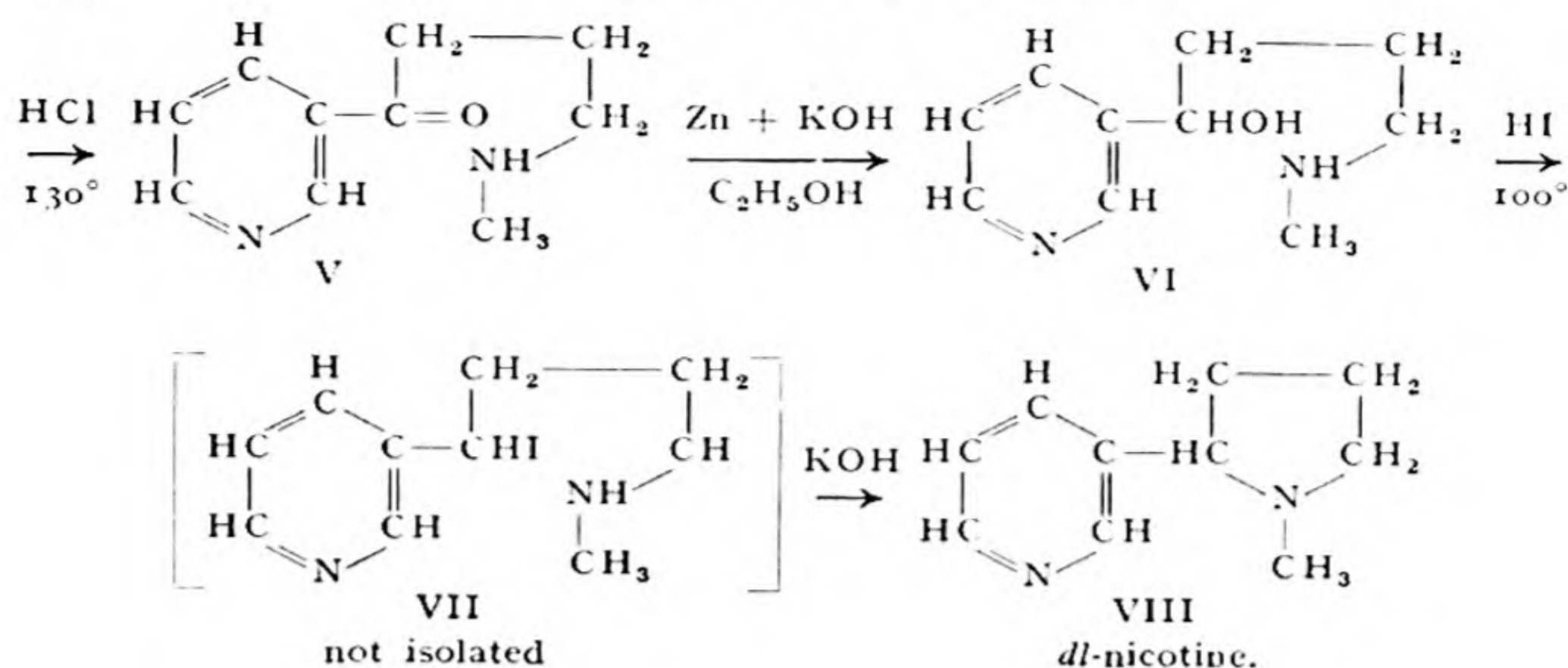
By oxidation with potassium permanganate or chromic acid, nicotinic acid (335) is produced. When the mono-methiodide of nicotine, carrying the quaternary group in the pyridine ring, is oxidised with potassium ferricyanide and alkali (compare 332), *N*-methylnicotone is produced, which may be converted by further oxidation into *l*-hygric acid (KARRER):



From this it follows that in nicotine, a pyridine ring is attached at the 3-position to the 2-position of an N-methylpyrrolidine nucleus and also, that naturally occurring *l*-nicotine has the same steric configuration as *l*-hygric acid and hence as *l*-proline (199, 314).

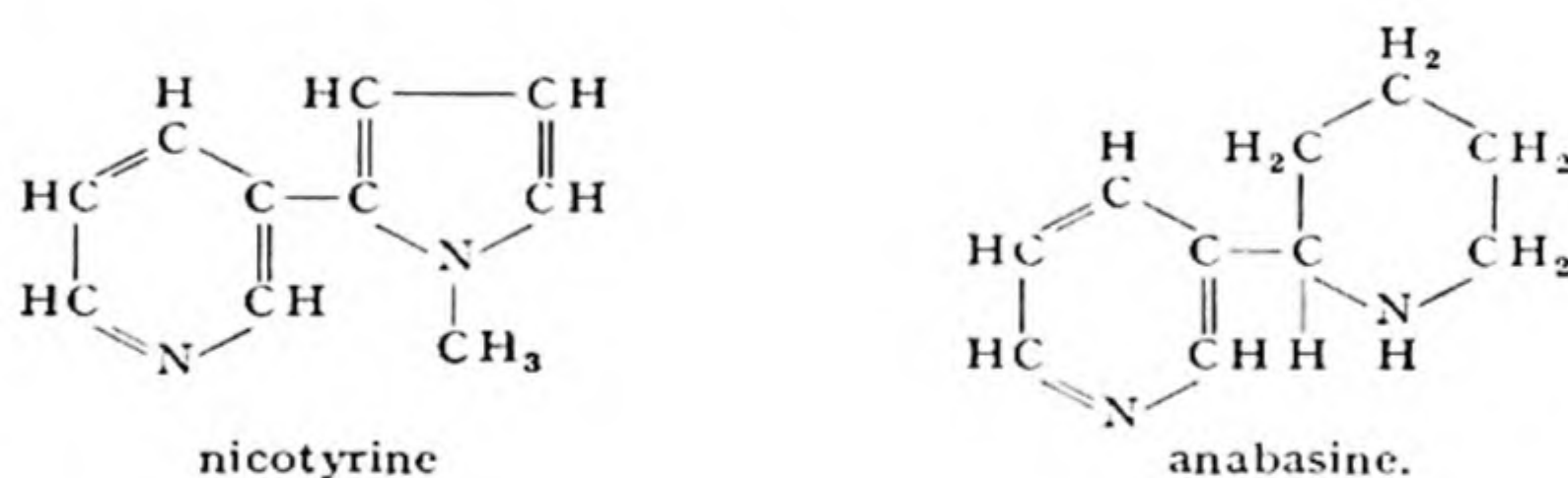
Synthesis of nicotine. A synthesis of nicotine was given in 1904 by A. PICTET, but investigations carried out by SPÄTH and KAINRATH and by WIBAUT and GITSELS showed that this synthesis was *not* conclusive, so that a later synthesis due to SPÄTH is given below. Electrolytic reduction of methylsuccinimide (I) gives N-methylpyrrolidone (II), which is converted into IV by condensation with ethyl nicotinate (III) under the influence of sodium ethoxide. By heating with hydrochloric acid, the bond between the $>\text{CO}$ - and $>\text{NCH}_3$ -groups in the pyrrolidone IV, is broken with the addition of a molecule of water; the intermediate product then loses carbon dioxide with the production of V. By reduction with zinc, caustic potash and alcohol, the latter is converted into the corresponding hydroxy-compound VI. By heating with hydriodic acid at 100° , the hydroxyl-group is replaced by iodine (VII) and finally, by heating with caustic potash solution, ring-closure takes place with the elimination of hydrogen iodide and the production of *dl*-nicotine (VIII):





Anabasine $\text{C}_{10}\text{H}_{14}\text{N}_2$ is isomeric with nicotine and occurs in *anabasis aphylla* a plant from the steppes (ORECHOFF) and also in *nicotiana glauca*. It has been identified as *3-pyridyl-2-piperidine*. It differs from nicotine in that the N-methylpyrrolidine-ring (314) is replaced by a piperidine residue. Anabasine is a liquid boiling at 276° and is laevo-rotatory $[\alpha]_D^{18} = -82.4^\circ$.

Nicotyrine $\text{C}_{10}\text{H}_{10}\text{N}_2$ (b.p. 281°) is produced by oxidising nicotine with silver oxide (BLAU); this compound can be more easily prepared, however, by passing nicotine vapour at 320° over finely divided platinum, whereby two molecules of hydrogen are split off (WIBAUT and OVERHOFF). Hence this alkaloid has the annexed structure:



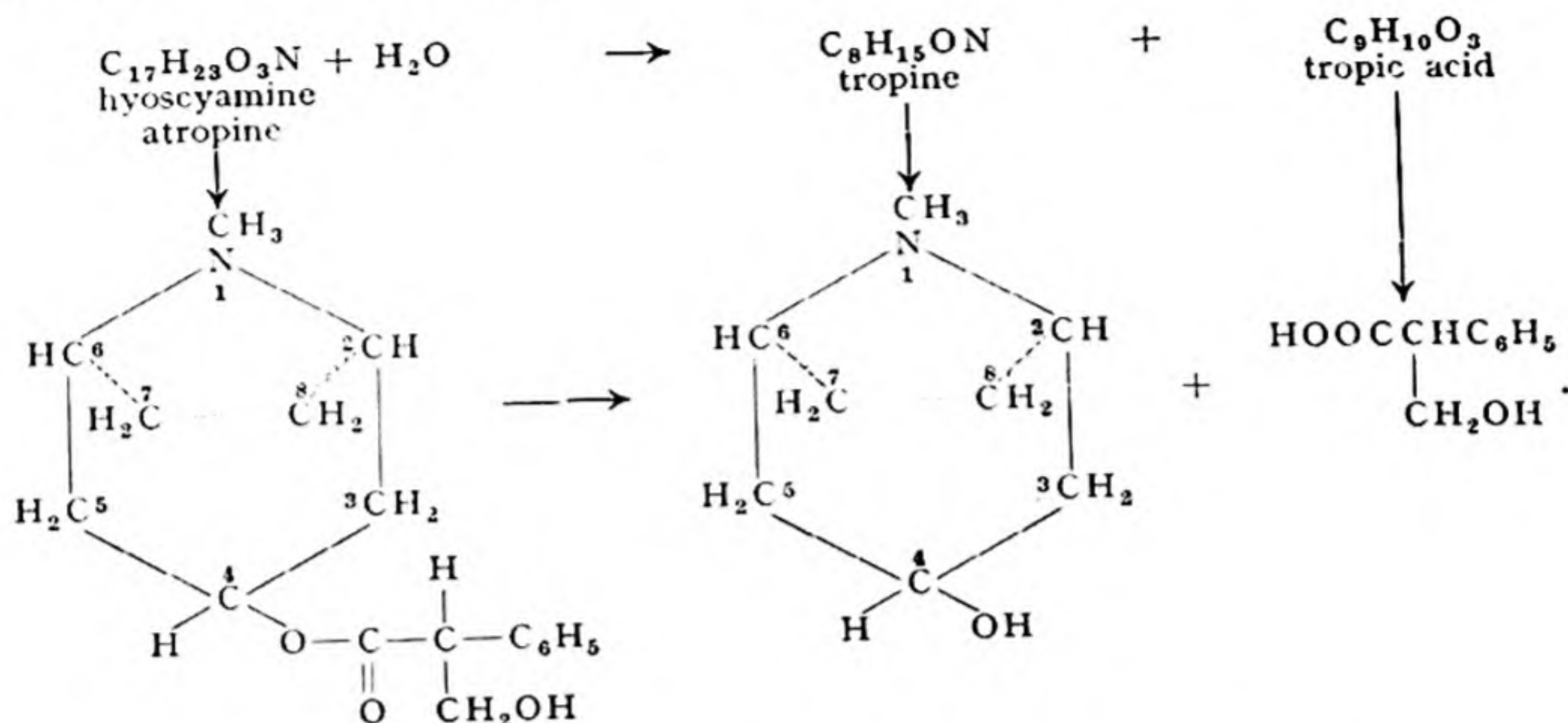
Alkaloids with condensed ring-systems (pyrrolidine and piperidine rings)

357. *Hyoscyamine* $\text{C}_{17}\text{H}_{23}\text{O}_3\text{N}$ was discovered in 1833 by GEIGER and HESSE; it occurs in various plants of the solanaceae family including *atropa belladonna*, *datura stramonium*, *hyoscyamus niger*. It melts at 108.5° and in solution in 50 % alcohol it shows a laevo-rotation $[\alpha]_D = -22^\circ$.

By the action of dilute alkalis, hyoscyamine is converted into a racemic *dl*-form melting at 118° , which is known as *atropine*. Atropine is used in medicine because of its "mydriatic action", *i.e.* it causes the pupil of the eye to dilate when a drop of a dilute solution of the alkaloid is allowed to fall into the eye. *l*-Hyoscyamine has a similar action.

Structure of hyoscyamine and atropine. By warming with dilute acids or alkalis, hyoscyamine is split up into tropine, which is optically inactive,

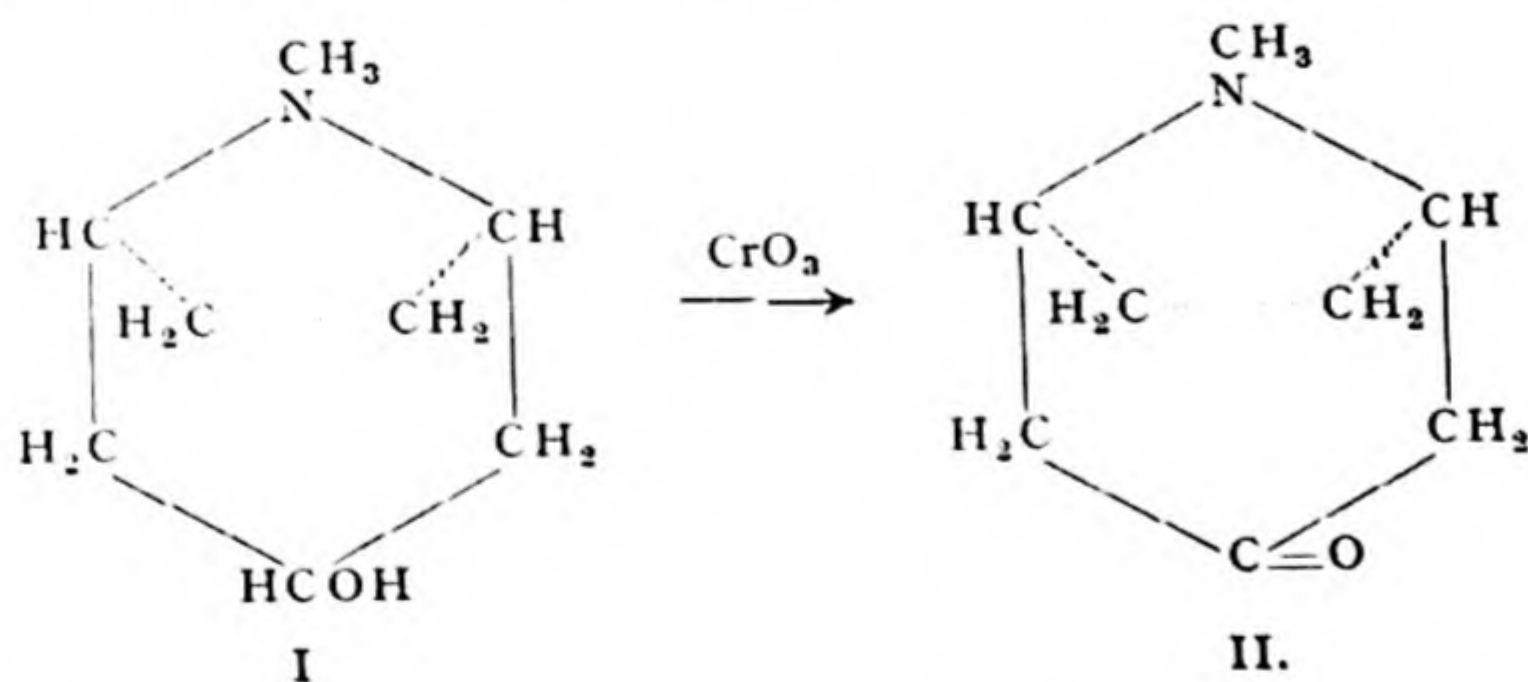
and *dl*-tropic acid (265). When, however, the hydrolysis is carried out with water at ordinary temperatures, *l*-tropic acid, which is very readily racemised, is produced. From this it follows that the optical activity of *l*-hyoscyamine must be ascribed to the tropic acid residue and that this part of the molecule is racemised when *l*-hyoscyamine is converted into atropine:



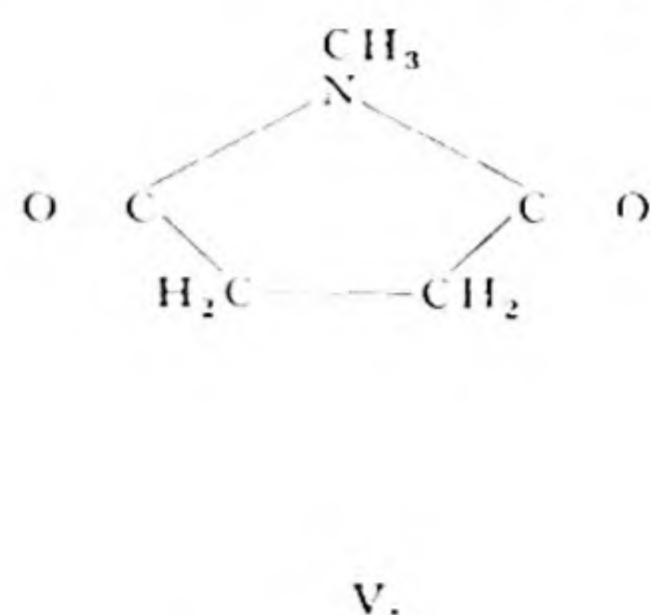
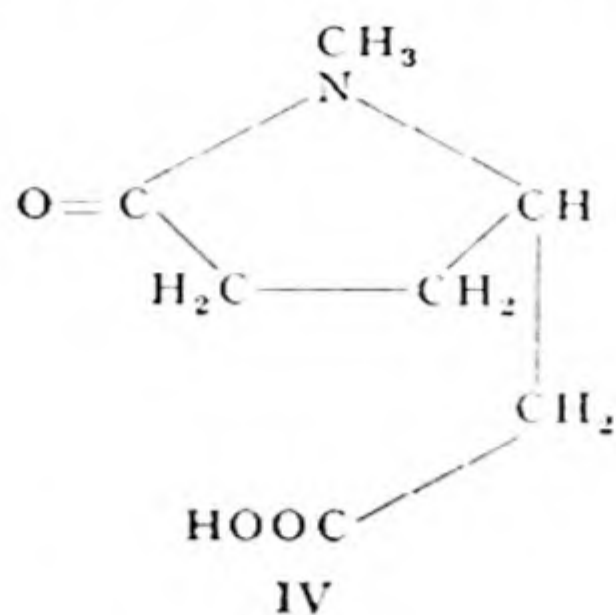
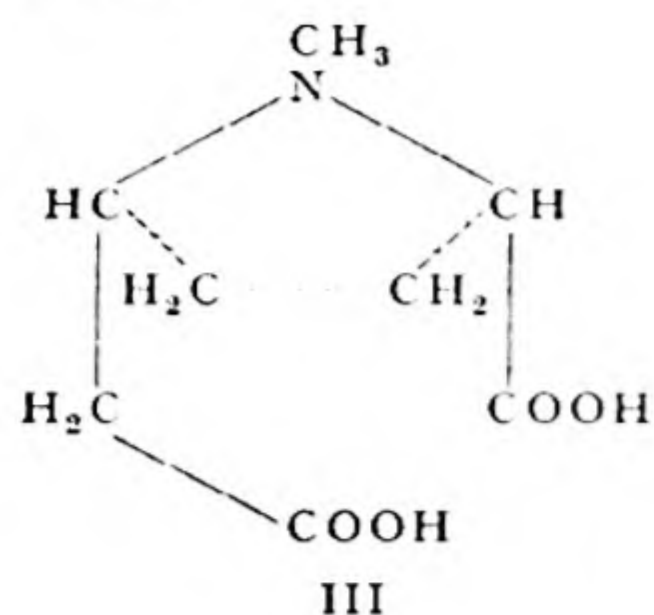
As will appear in the determination of the structure of tropine, this compound possesses an alcoholic hydroxyl group so that hyoscyamine is an ester of tropine and tropic acid.

Structure of tropine. This has been elucidated by the researches of LADENBURG, MERLING and WILLSTÄTTER, the formula being suggested by the latter investigator.

A ketone, *tropinone* $\text{C}_8\text{H}_{13}\text{ON}$ (II), is produced by the oxidation of tropine (I) with chromic acid in acid solution:



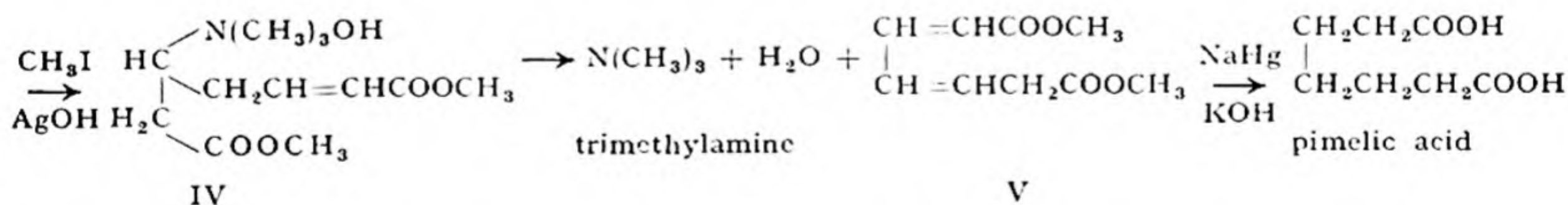
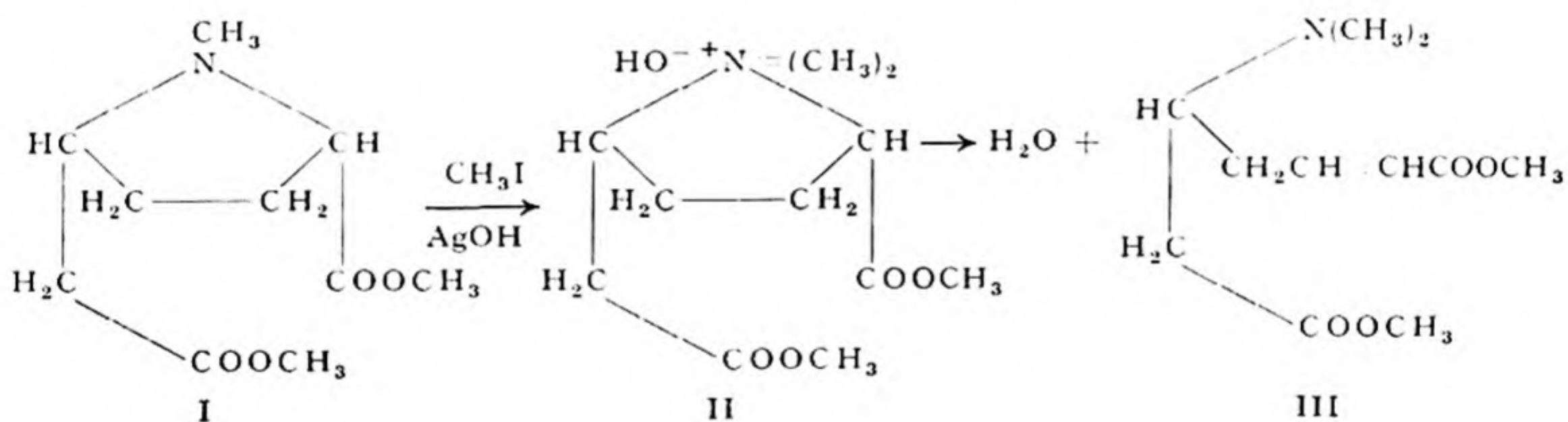
With amyl nitrite, this compound gives a di-isonitroso-compound. Hence the carbonyl group must lie between two $-\text{CH}_2$ groups; a hydrogen atom in each of these groups must be replaced by a $=\text{NOH}$ group. When tropinone is oxidised further, tropic acid (III) is formed first of all along with ecgoninic acid (IV) and finally N-methylsuccinimide (V) (see 125):



From the formation of V it follows that a pyrrolidine-ring (314) is present in tropine.

The structure of tropic acid has been proved by a degradation method, which has also been applied to other compounds containing a nitrogen atom combined in the ring.

By methylating methyl tropate (I), a quaternary ammonium salt is formed. The base obtained from this salt (II), on heating, loses a molecule of water with the formation of the olefinic compound III:

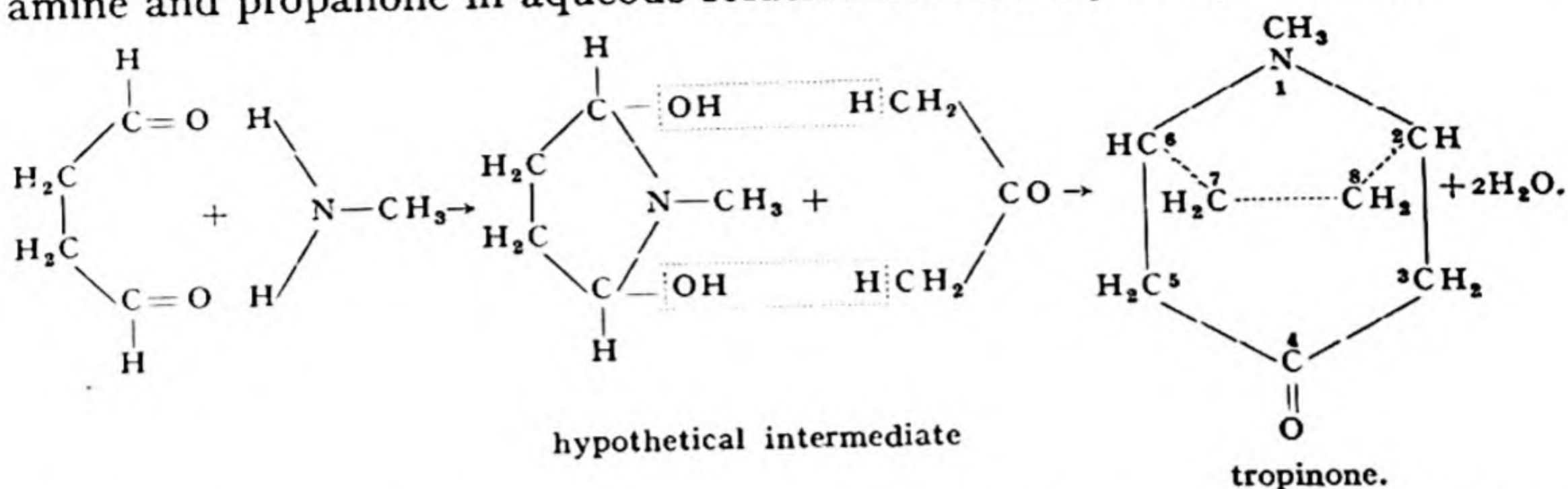


By methylation and treatment with silver hydroxide, the base IV is produced, which decomposes on heating into trimethylamine, water and the ester of the unsaturated acid V, containing two double bonds. This acid is converted into pentane 1,5-dicarboxylic acid or pimelic acid on reduction with sodium amalgam in an alkaline medium.

From the above, it follows that there is a ring of seven carbon atoms with a nitrogen bridge between carbon atoms 2 and 6, present in both tropine and tropinone. The structure of tropine may also be regarded as a condensed ring-system composed of a *non-planar* piperidine-ring and a pyrroli-

dine-ring, having three atoms in common as shown schematically in the formulae.

The structure of tropinone was confirmed by a most interesting synthesis by R. ROBINSON. This depends on the condensation of butanedial, methylamine and propanone in aqueous solution at ordinary temperatures:



Two asymmetric carbon atoms (2 and 6), which are mutually equivalent, occur in the tropinone molecule. Hence three stereoisomeric forms of tropinone are imaginable, namely, two mirror-image *d*- and *l*-forms and an inactive form, the molecule of which is symmetrical (compare *d*- and *l*- and meso-tartaric acids). In the symmetrical form, carbon atoms 7 and 8 are combined in the *cis*-position to the piperidine ring; a strain-free model can be constructed for this form (280, 288). In the asymmetric *d*- and *l*-forms, in which carbon atoms 7 and 8 are attached to the piperidine ring, in the *trans*-form, considerable strain should be present according to the space model. In accordance with this prediction, only one form of tropinone is known and this is symmetrical and inactive. For the same reason, the molecule of tropine is symmetrical; it possesses a plane of symmetry which can be drawn through atoms 1 and 4 and bisects the bond between 7 and 8. The hydrogen atom and the hydroxyl group on carbon atom 4 can take up two different positions in this plane. The hydroxyl group may stand in the *cis*- or the *trans*-position with respect to the carbon bridge 7-8. Both stereo-isomeric forms of tropine, both of which are inactive, are known. Tropine from hyoscyamine or atropine melts at 62° and boils at 233°.

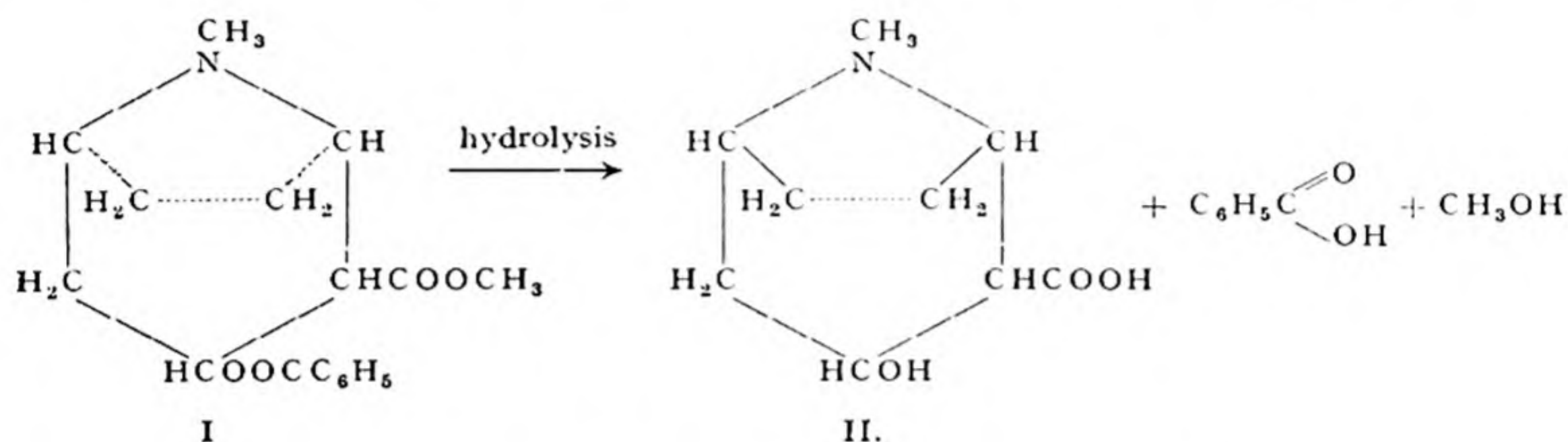
When tropinone is reduced with zinc dust and hydriodic acid, not only is tropine produced but also *pseudo*-tropine, which melts at 109° and which is unlike tropine in that it is not volatile in steam. Atropine is obtained by esterifying tropic acid with tropine; this constitutes a synthesis of this alkaloid.

358. Coca-alkaloids. Various closely related alkaloids, such as cocaine, cinnamylcocaine, benzoylecgonine, α - and β -truxilline and tropacocaine, some of which will be discussed in more detail, occur in the leaves of *erythro*-

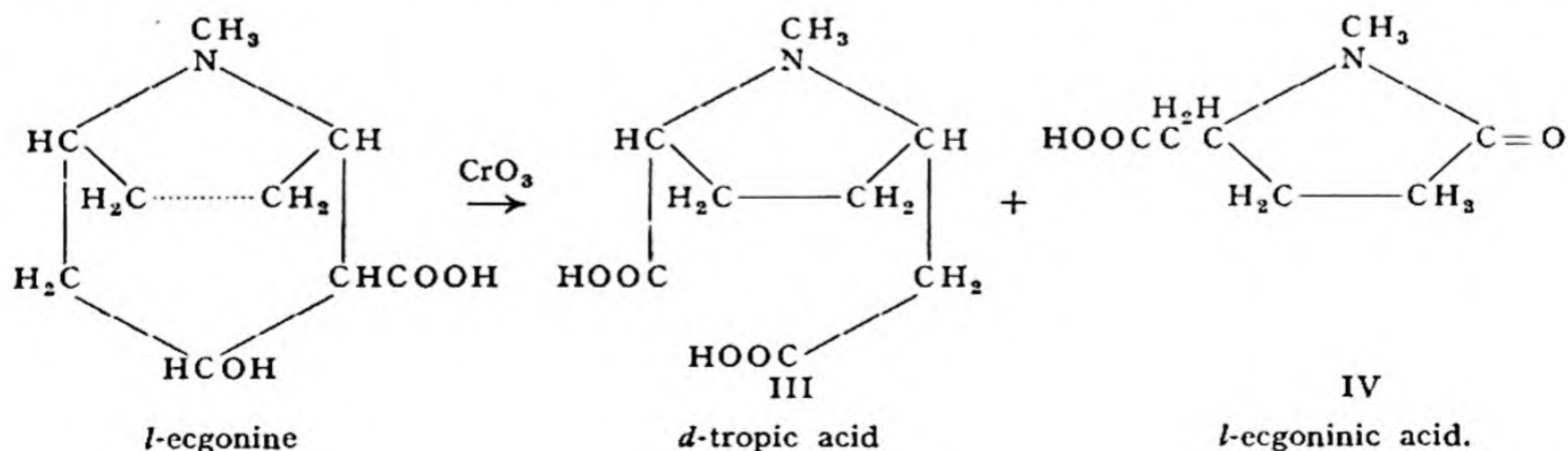
xylon coca. Along with these alkaloids, hygrine also occurs in South American coca-leaves (see 354).

Cocaine $C_{17}H_{21}O_4N$ is the most important alkaloid in this group. It was isolated by NIEMANN in 1860 from South American coca-leaves in which it occurs to the extent of 1.3 %. It is a crystalline compound, which melts at 98° and is sparingly soluble in cold water and readily soluble in alcohol; the solution is optically active $[\alpha]_D = -15.8^\circ$.

The structure of cocaine is closely related to that of tropine (357) as is shown by the following. When cocaine (I) is hydrolysed with concentrated acids, it gives benzoic acid(260), methyl alcohol and *ecgonine* $C_9H_{15}O_3N$ (II):

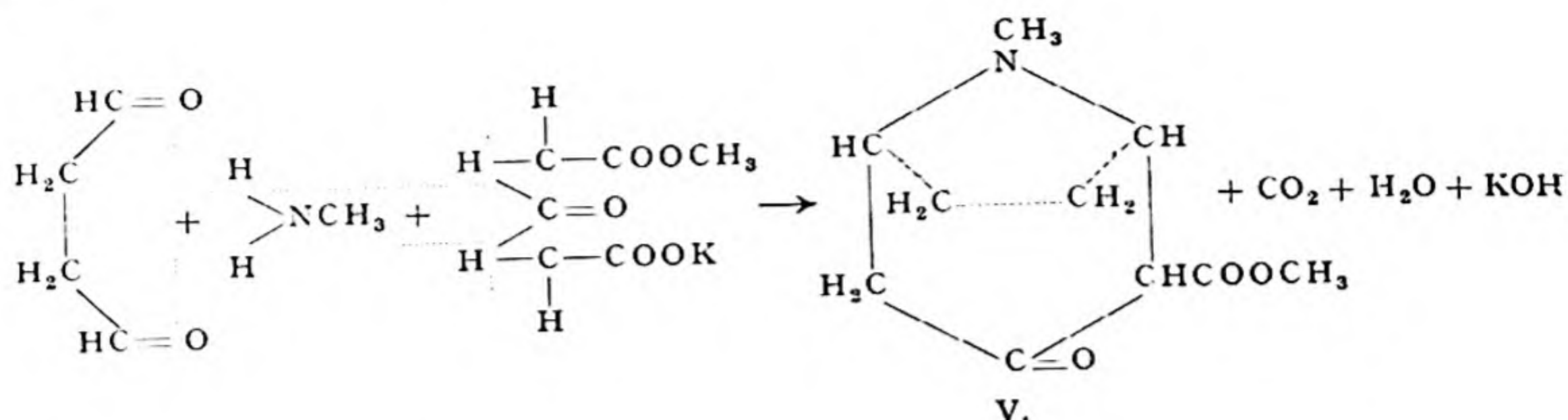


By treatment with methyl alcohol and hydrogen chloride, ecgonine can be converted into a methyl ester, which can be benzoylated with benzoyl chloride to produce cocaine. Thus ecgonine contains a carboxyl group and an alcoholic hydroxyl group. It also forms a salt with hydrochloric acid and therefore contains a basic group. The structure of ecgonine follows from the results of oxidation with chromic acid whereby tropic acid (III) and ecgoninic acid (IV) are formed, both of which can also be obtained by oxidising tropine. The difference is, however, that in the oxidation of optically active ecgonine the acids are also produced in an optically active form:

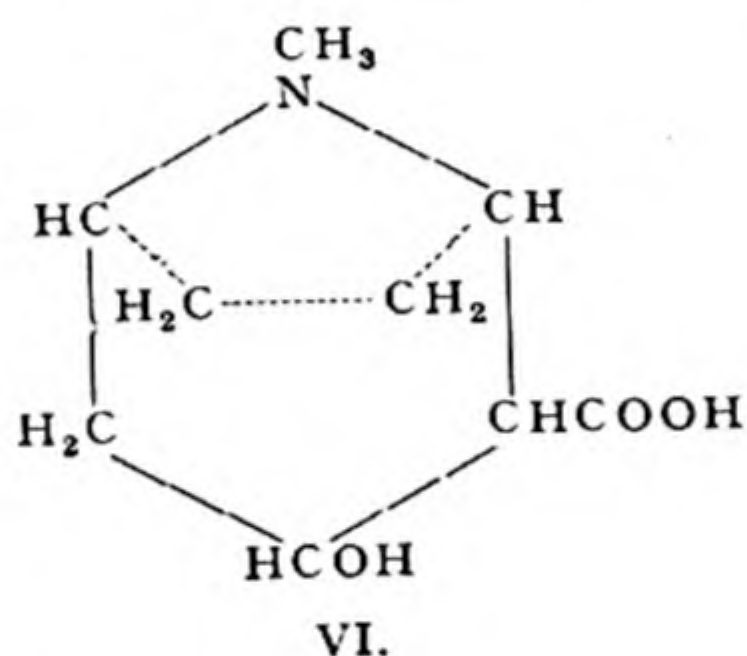


Ecgonine was prepared synthetically by WILLSTÄTTER. The methyl ester of *tropinone carboxylic acid* (V) is produced from butanedial, methylamine

and the potassium salt of the mono-methyl ester of acetone dicarboxylic acid:



On reduction and hydrolysis, V is converted into ecgonine (VI):

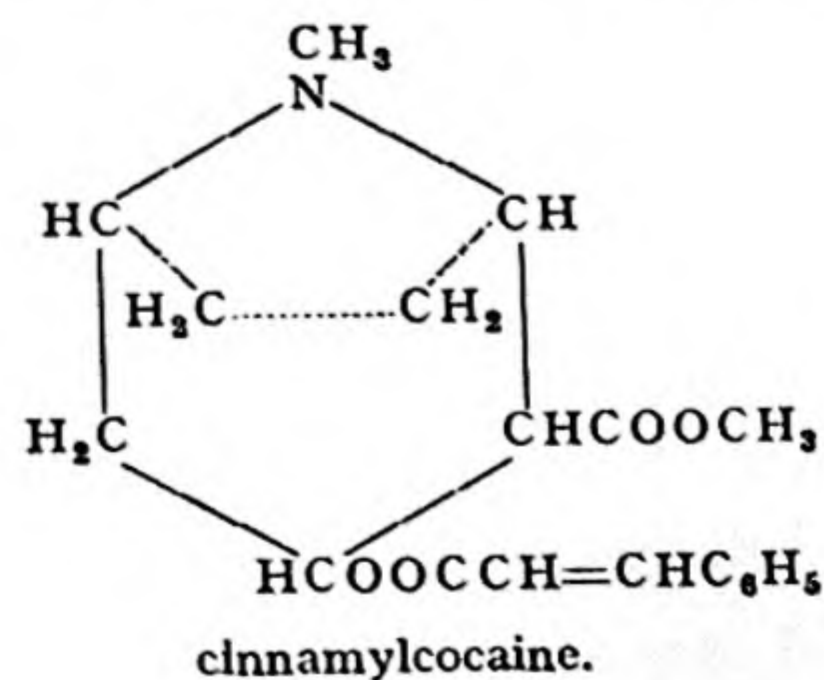


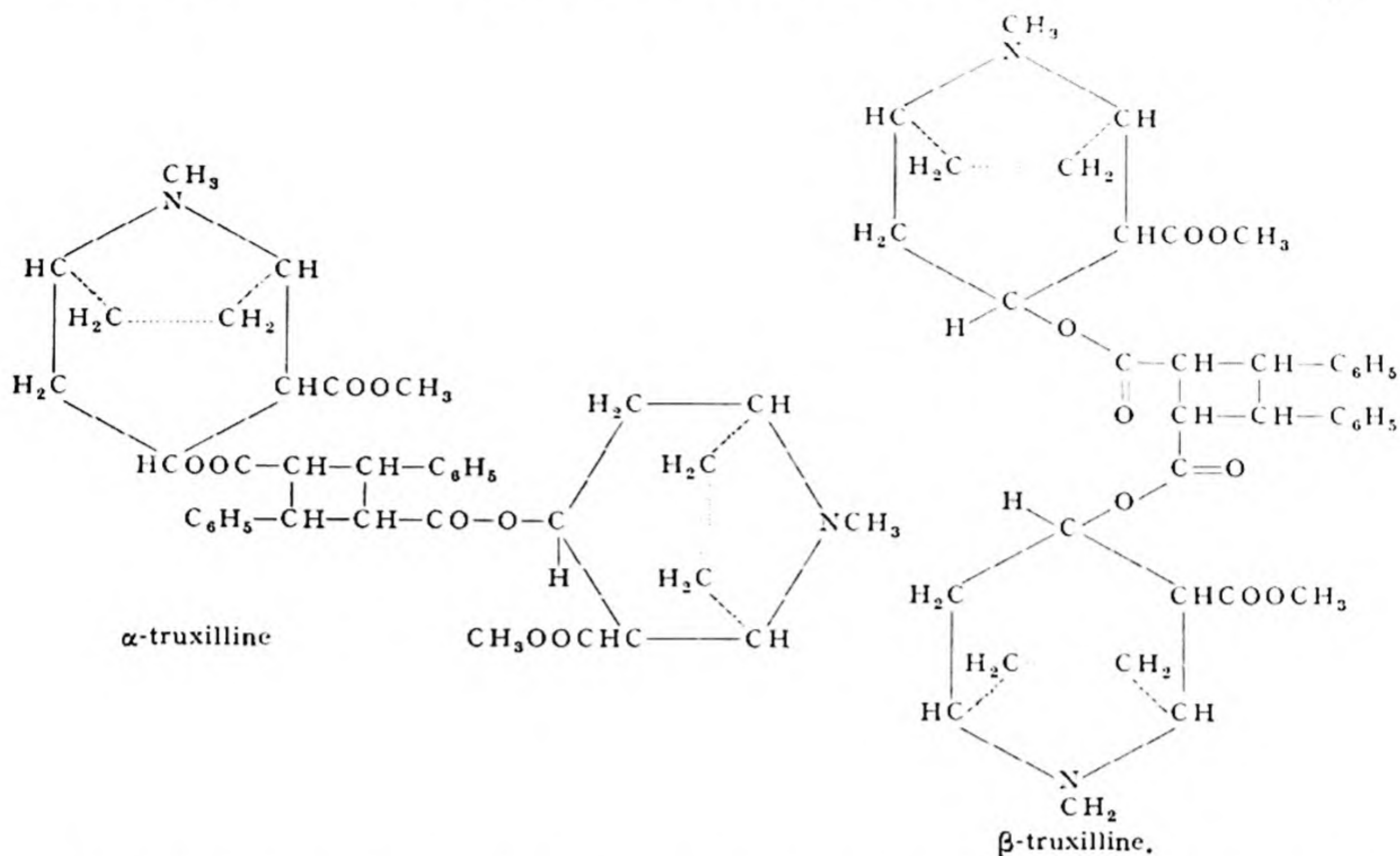
Ecgonine possesses four asymmetric carbon atoms; thus there ought to be sixteen stereo-isomers. Since, however, the $-\text{CH}_2-\text{CH}_2-$ bond on the piperidine ring occurs only in the *cis*-position, only eight isomers remain. Several of these eight isomers and the corresponding cocaines, are known.

There occurs in coca-leaves along with *l*-cocaine a small amount of *d*-pseudo-cocaine or *d*- ψ -cocaine melting at 47° . This isomer may be derived from *d*-ecgonine produced by heating naturally occurring ecgonine with caustic potash solution.

Cinnamylcocaine $\text{C}_{19}\text{H}_{23}\text{O}_4\text{N}$, melting at 121° , $[\alpha]_D = -4.7^\circ$ (in chloroform), occurs in Japanese coca-leaves; on acid hydrolysis it gives *l*-ecgonine, cinnamic acid (268) and methanol. It can be prepared from the methyl ester of *l*-ecgonine and cinnamyl chloride. From this its structure must be represented by the annexed formula:

α - and β -*Truxilline* $\text{C}_{38}\text{H}_{46}\text{O}_8\text{N}_2$ on hydrolysis give two mols of *l*-ecgonine, two mols of methanol and one mol. of α - or β -*truxillic acid*, respectively (these are dimers of cinnamic acid). They have no anaesthetic action.



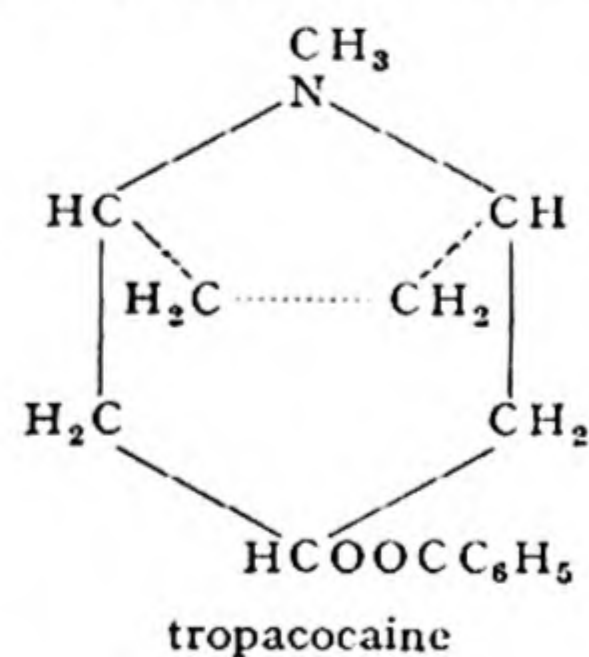


In technical practice it is usual to break down the total coca-alkaloids from the plant material to ecgonine, which is then converted into cocaine by esterification and benzylation. On account of its anaesthetic properties cocaine is used as a local anaesthetic.

A large number of compounds have been prepared as substitutes for cocaine. It has been found that both the hydroxyl group and the carboxyl group in ecgonine must be esterified; the ethyl ester of benzoylecgonine *cocaethylene* as well as the corresponding propyl and butyl esters are powerful anaesthetics. The benzoyl group is also necessary for anaesthetic action.

Benzoates and *p*-aminobenzoates of some of the simpler aliphatic aminoalcohols also possess anaesthetic action (compare novocaine 262).

Tropacocaine $C_{15}H_{19}O_2N$ occurs in Javanese coca-leaves. From its structure it belongs to the atropine group, for it is the benzoate ester of ψ -tropine. It melts at 49° , has powerful anaesthetic properties and can be obtained synthetically by benzoylating ψ -tropine (357).



Alkaloids with a quinoline ring

359. Cinchona alkaloids. A collection of different alkaloids (at least 24), of which *quinine* and *cinchonine* are the most important, occurs in the inner and outer bark of trunks, branches and roots of trees belonging to the cinchona species of the rubiaceae family.

From South America, where the cinchona tree is indigenous, it was introduced into Java where it is now cultivated on a large scale.

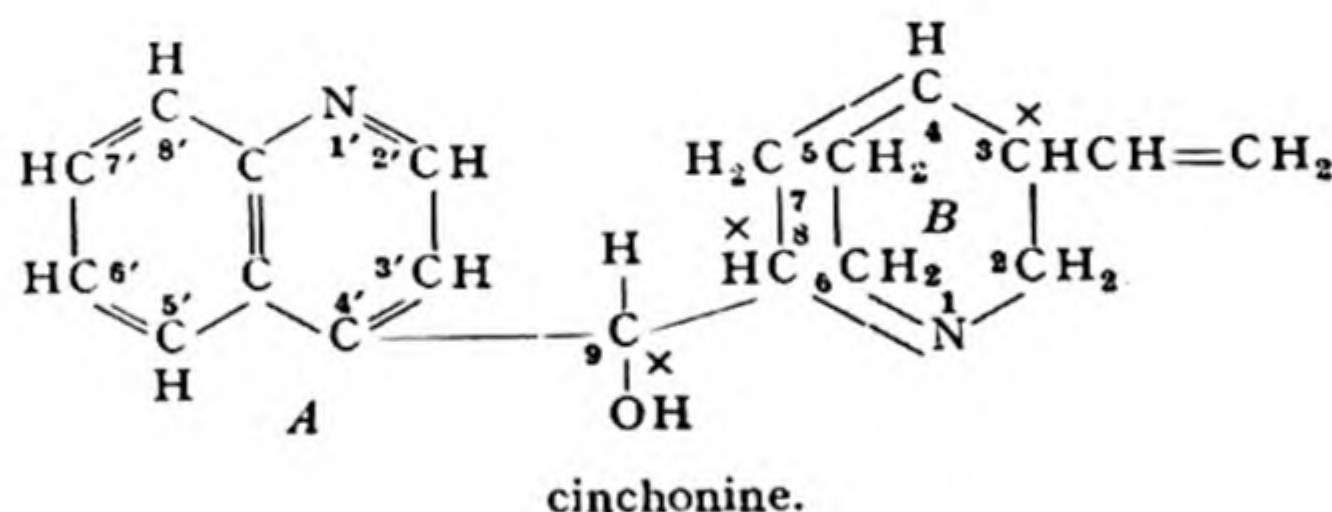
The name *Cinchona* was given to this species by LINNEAUS in 1742.

Cinchonine $C_{19}H_{22}ON_2$ melts at 260° , has $[\alpha]_D = 224.4^\circ$ and is sparingly soluble in water and alkalis but readily soluble in acids, alcohol and chloroform. A number of cinchonine salts are known, e.g. $(C_{19}H_{22}ON_2)_2H_2SO_4 \cdot 2aq.$, $(C_{19}H_{22}ON_2)HCl \cdot 2aq.$, etc.

Cinchonine has febrifugal properties and like quinine, is used as a drug against malaria.

Structure of cinchonine and quinine. This has been elucidated by the work of various investigators including SKRAUP, KÖNIGS and RABE. In the structural formula of cinchonine, which was suggested by RABE, the molecule contains a quinoline-ring (A) and a bicyclic hydrogenated ring-system (B) for which KÖNIGS has suggested the name of *quinuclidine*. The oxidation products from this part of the molecule are indicated by the prefix *mero-* (from $\mu\epsilon\rho\omicron\varsigma$ = part) or by the word *loipo-* (from $\lambda\omicron\iota\pi\omicron\varsigma$ = remainder).

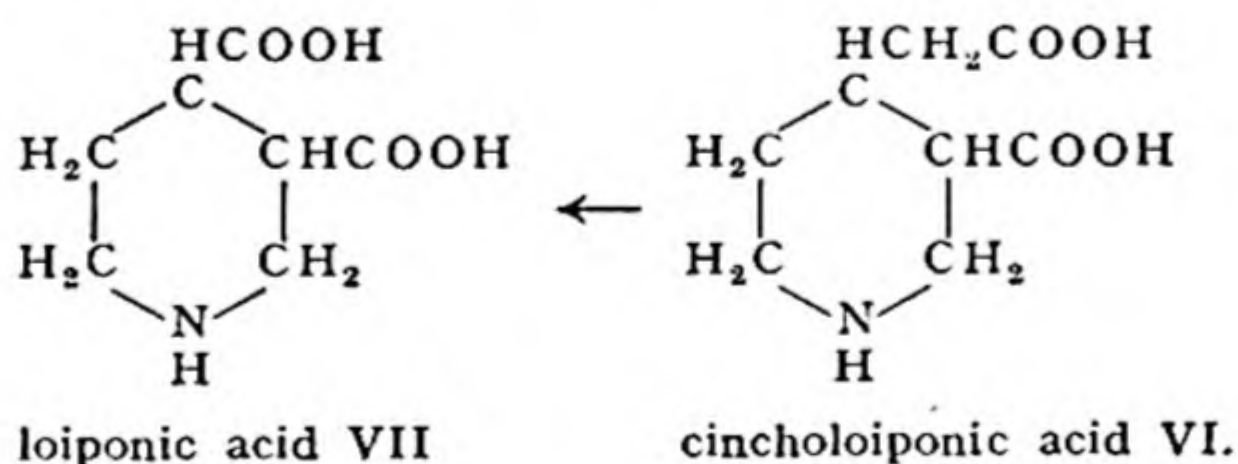
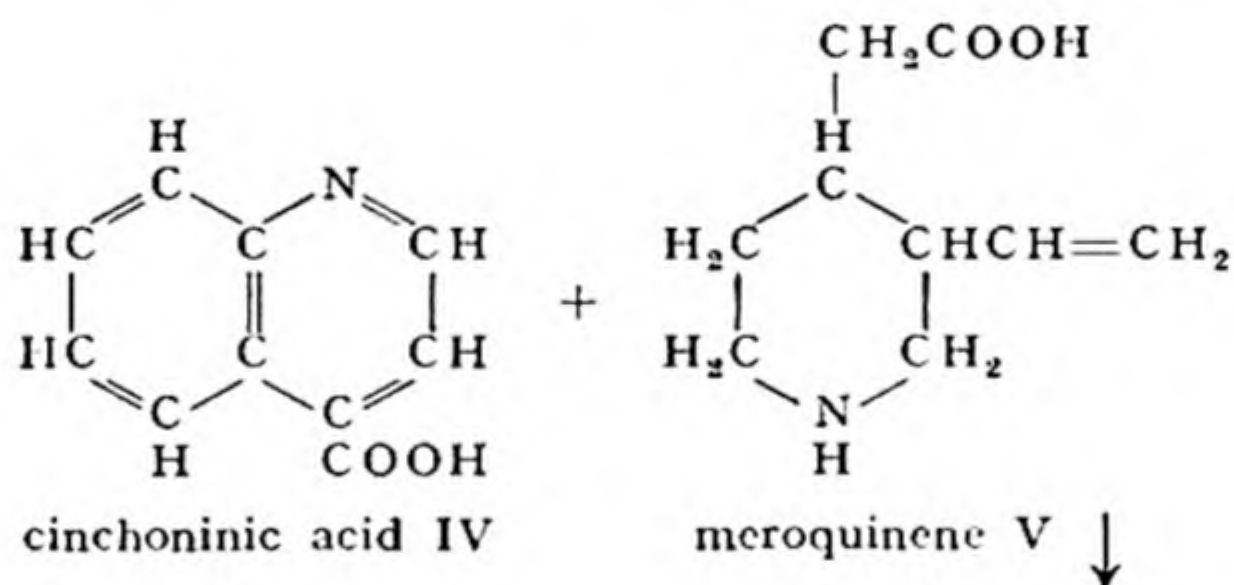
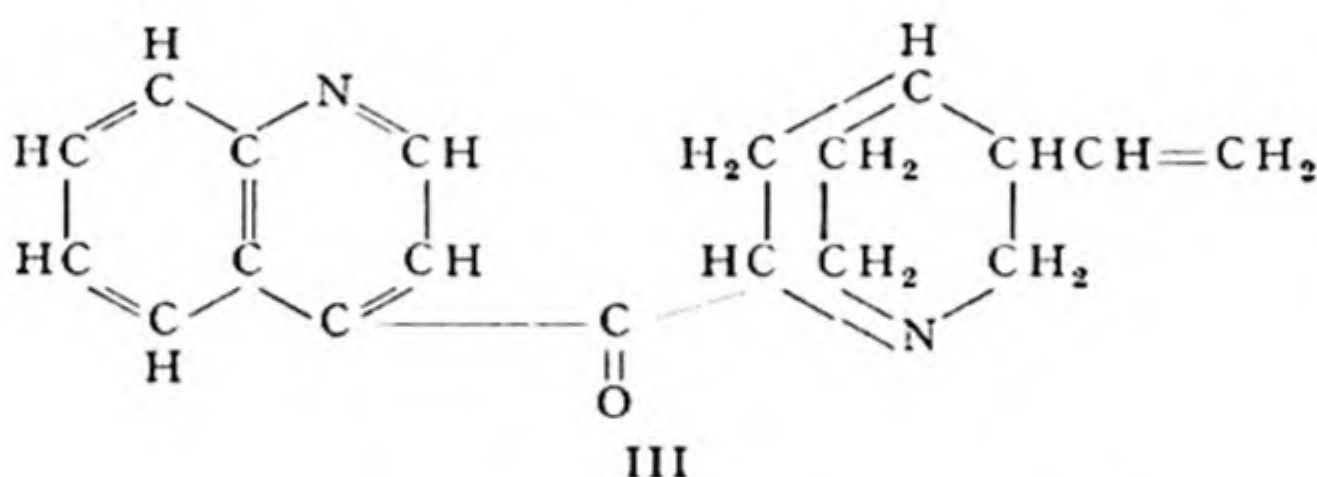
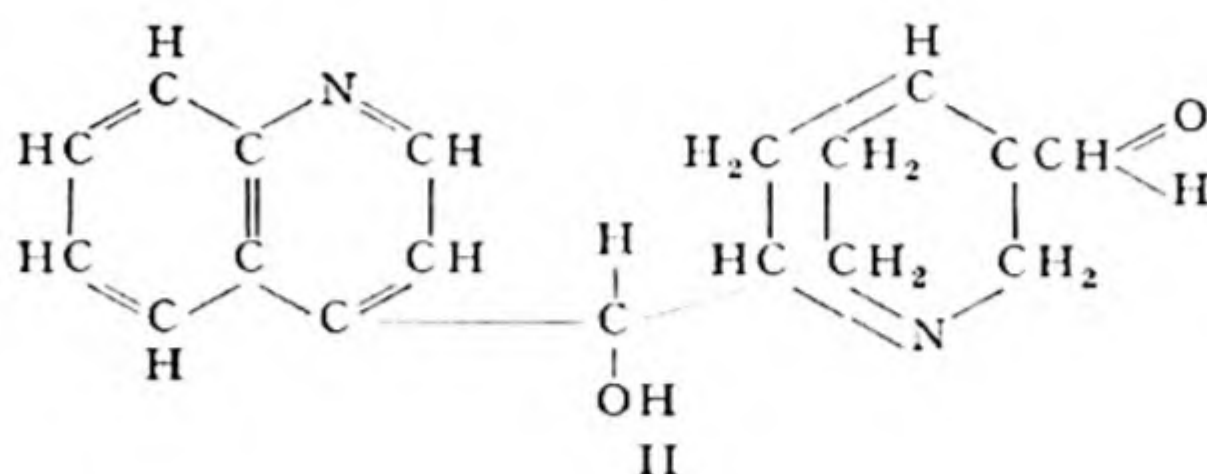
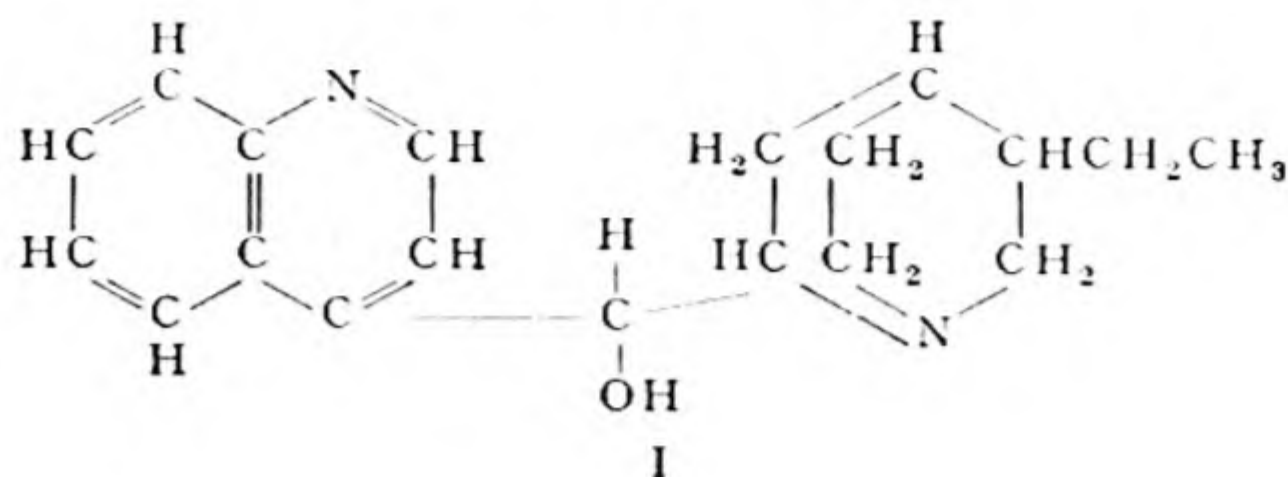
There are four asymmetric carbon atoms in cinchonine, namely, 3, 4, 8 and 9, which give rise to the possibility of 16 stereo-isomerides.



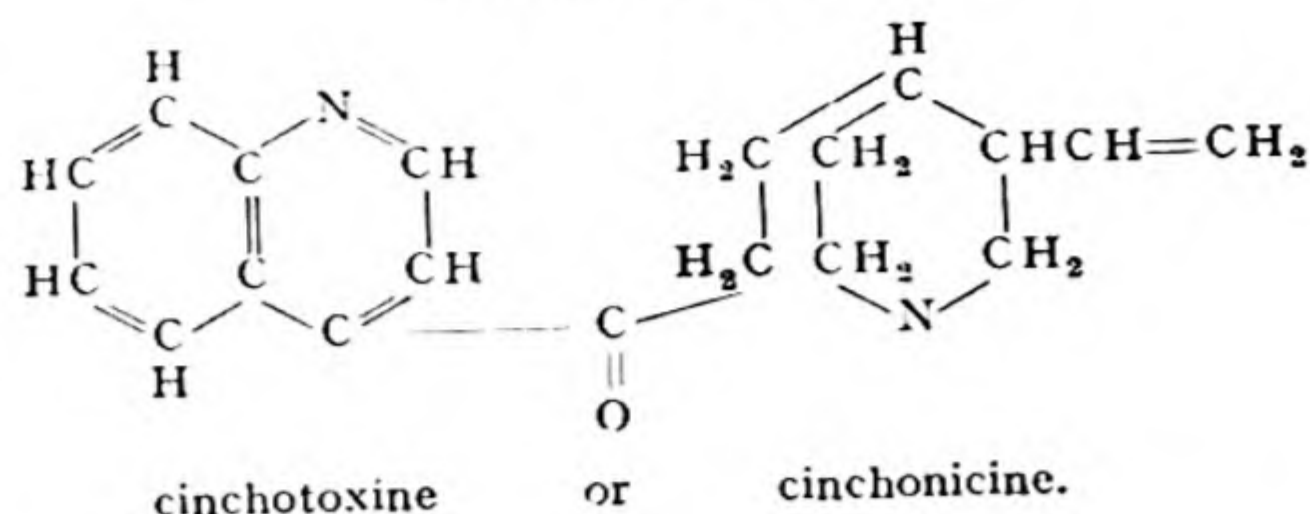
The structural formula for cinchonine takes into account the reactions as shown above.

By catalytic reduction, cinchonine can be converted into *dihydrocinchonine* $C_{19}H_{24}ON_2$ (I); formaldehyde and an aldehyde *cinchoninal* $C_{19}H_{20}O_2N_2$ (II) is formed by the action of ozone and decomposition of the resultant ozonide with water (SEEKLES). From this it follows that a vinyl group is present in cinchonine. By moderate oxidation with chromic acid, a ketone *cinchoninone* $C_{19}H_{20}ON_2$ (III) is produced from cinchonine; the oxygen must be present therefore as a secondary alcohol grouping.

Further oxidation of cinchonine with chromic acid produces quinoline 4-carboxylic acid (IV) or cinchoninic acid and *meroquinene* (V), which is also an acid and which is converted by subsequent oxidation into *cincholoiponic acid* (VI) and finally, into *loiponic acid* (VII) (SKRAUP and KÖNIGS):

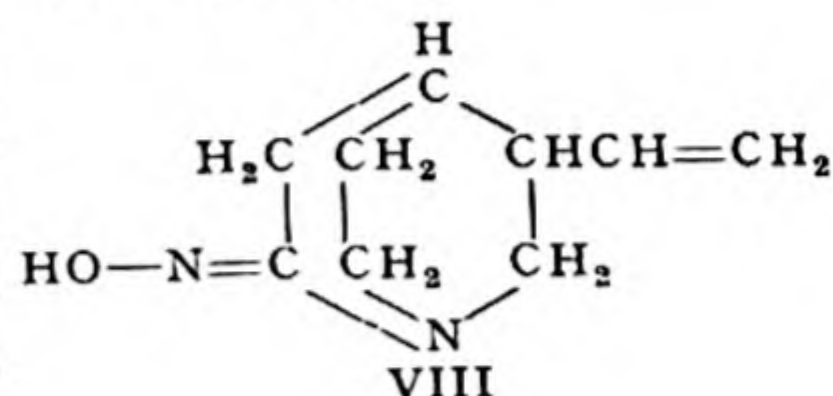


When cinchonine is warmed with acetic acid and phosphoric acid it is converted into an isomeric compound *cinchonidine* or *cinchotoxine* containing a ketone group. This reaction, known as *hydraminic fission*, frequently occurs in compounds carrying a hydroxyl group and an amino-like nitrogen atom on neighbouring carbon atoms.

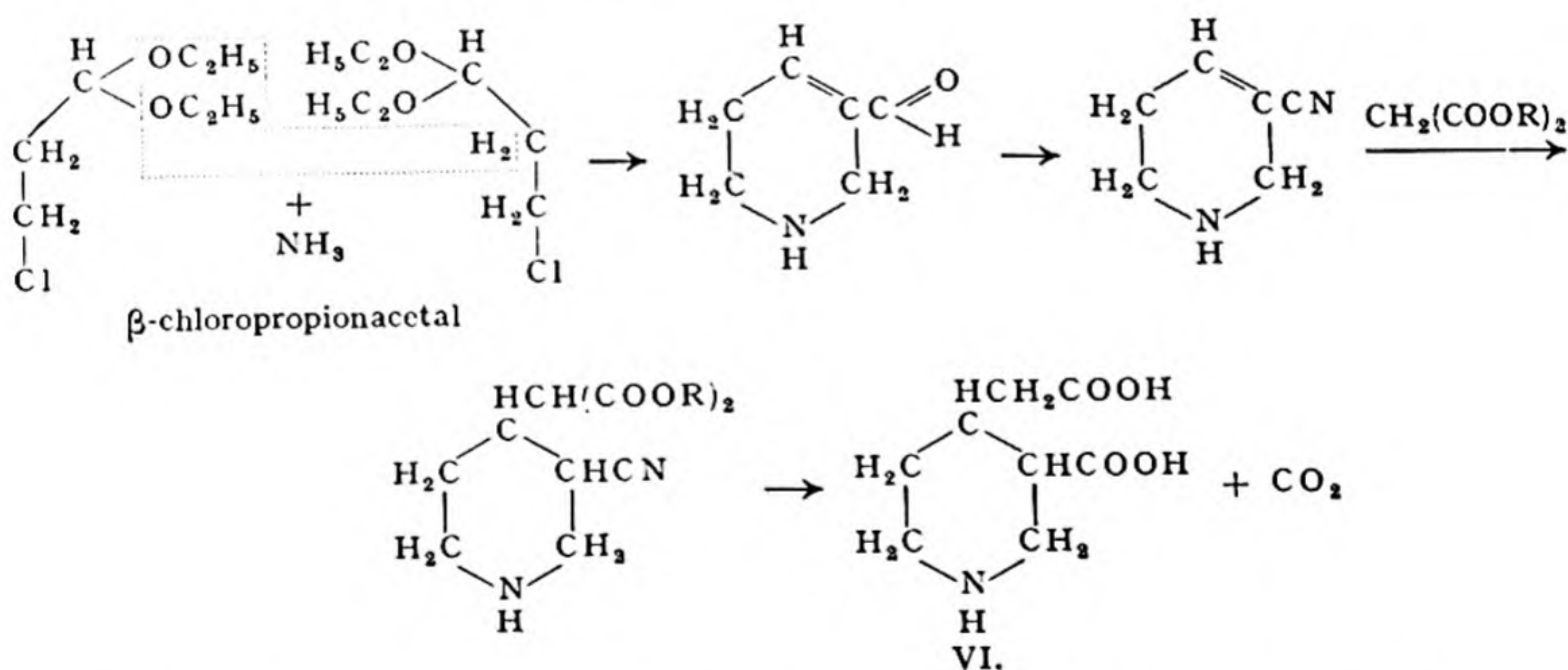


This ketone is probably an intermediate product in the oxidative fission of cinchonine into meroquinene (V) and cinchoninic acid (IV).

By the action of nitrous acid on cinchoninone (III), cinchoninic acid (IV) is produced in a 90% yield and the *oxime* of β -vinylquinuclidone (VIII) in a yield of 75% (RABE). Compound VIII, which is derived from the quinuclidine-ring system, is converted into meroquinene (V) by hydrolysis.

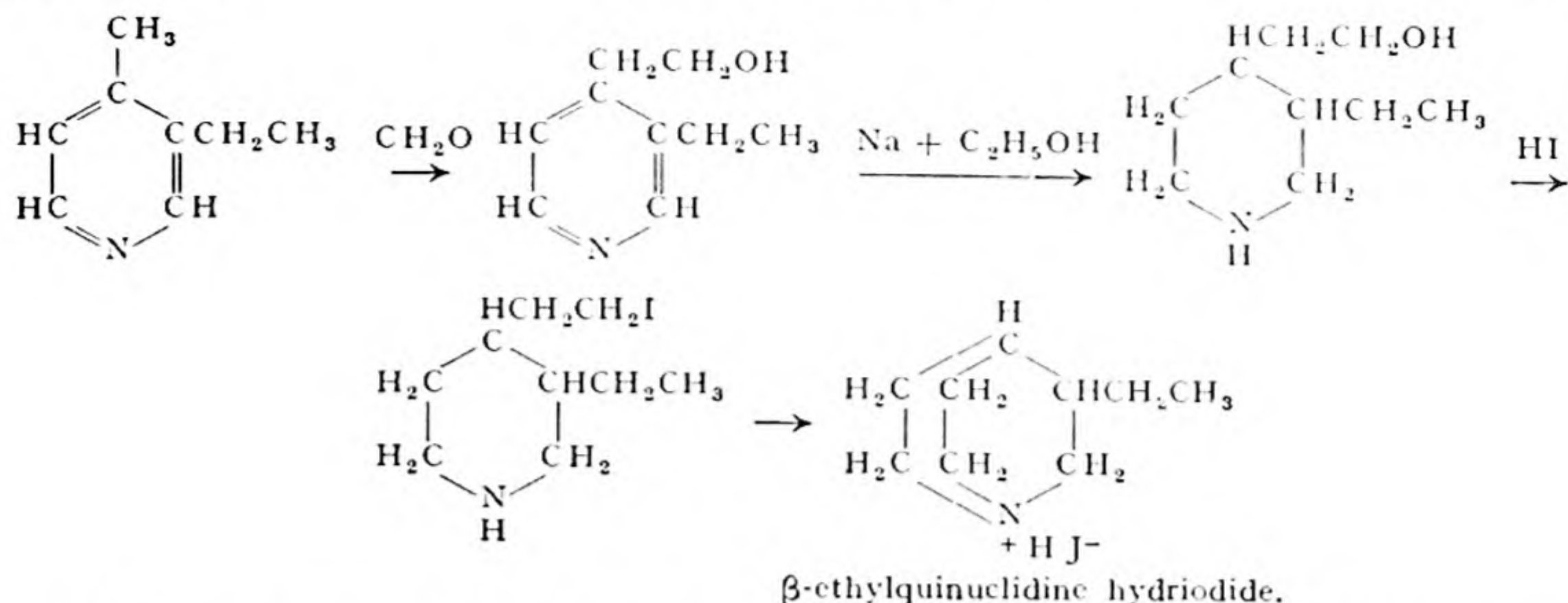


The structure of the above-mentioned degradation products has been confirmed by synthesis. Cinchoninic acid (IV) was obtained from quinoline (337) (KAUFMANN). For the synthesis of cincholoiponic acid (VI), WOHL condensed β -chloropropionacetal with ammonia to give a tetrahydropyridine- β -aldehyde, which was converted into the corresponding nitrile via the oxime. Ethyl malonate was then added on to the double bond and VI was eventually obtained from the addition product by hydrolysis and elimination of carbon dioxide:



Since VI is converted into 4-methylpyridine (γ -lepidine) by heating with concentrated sulphuric acid, it is proved that the $-\text{CH}_2\text{COOH}$ group is attached to carbon atom 4.

β -Ethylquinuclidine has also been obtained synthetically. *Methylol- β -collidine* is produced from 3-ethyl-4-methylpyridine or β -collidine (333) by condensation with formaldehyde. After reduction and treatment with hydriodic acid, an iodide is produced, which passes over directly into the hydriodide of β -ethylquinuclidine:

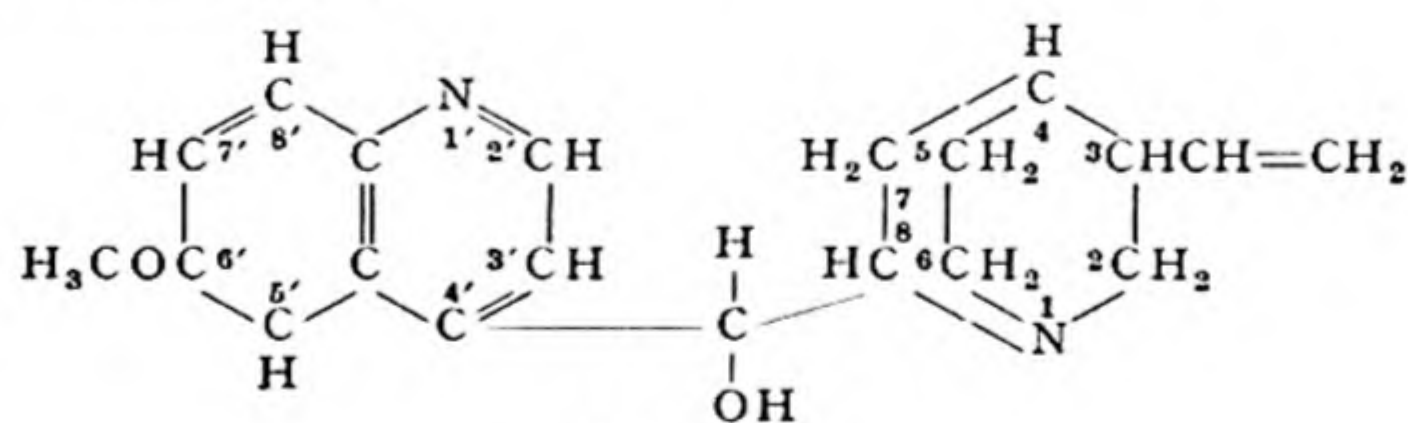


Dihydrocinchonine has been prepared synthetically by RABE so that the structure has been completely established.

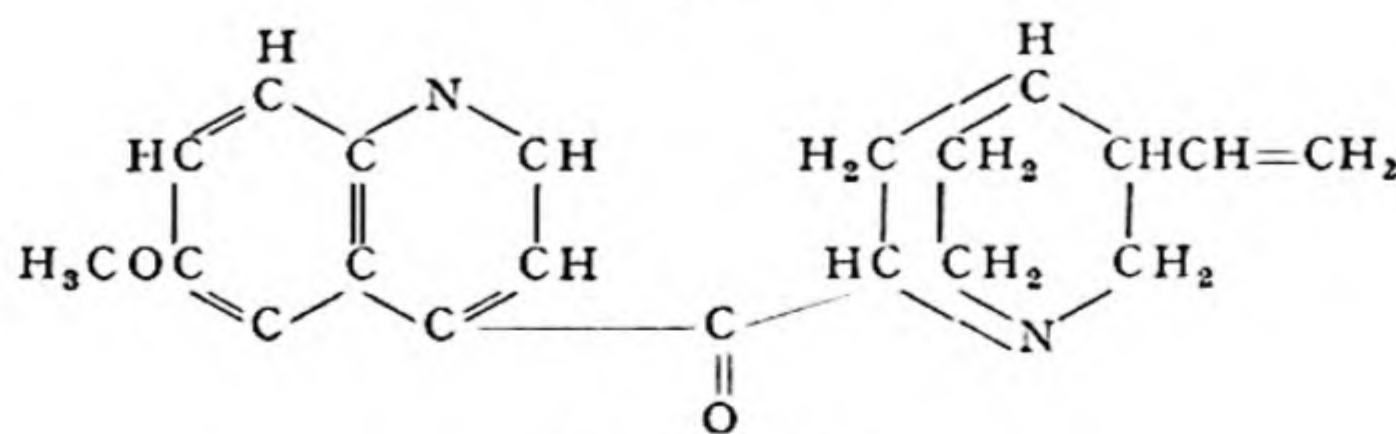
360. Quinine $C_{20}H_{24}O_2N_2$ is the most important alkaloid of this group. It melts at 177° when anhydrous and the trihydrate melts at 57° ; $[\alpha]_D = -158.2^\circ$ (in 99 % alcohol). It is sparingly soluble in water, more soluble in ether and readily soluble in alcohol and chloroform. Various salts of quinine are known, including the neutral sulphate $(C_{20}H_{24}O_2N_2)_2H_2SO_4 \cdot 8H_2O$, which fluoresces pale blue in aqueous solution and a stronger blue in dilute sulphuric acid solution, the acid sulphate $C_{20}H_{24}O_2N_2 \cdot H_2SO_4 \cdot 7H_2O$, the hydrochloride $C_{20}H_{24}O_2N_2HCl \cdot 2H_2O$.

Quinine is used as a febrifuge; the great importance of quinine as a drug lies in its specific action against malaria.

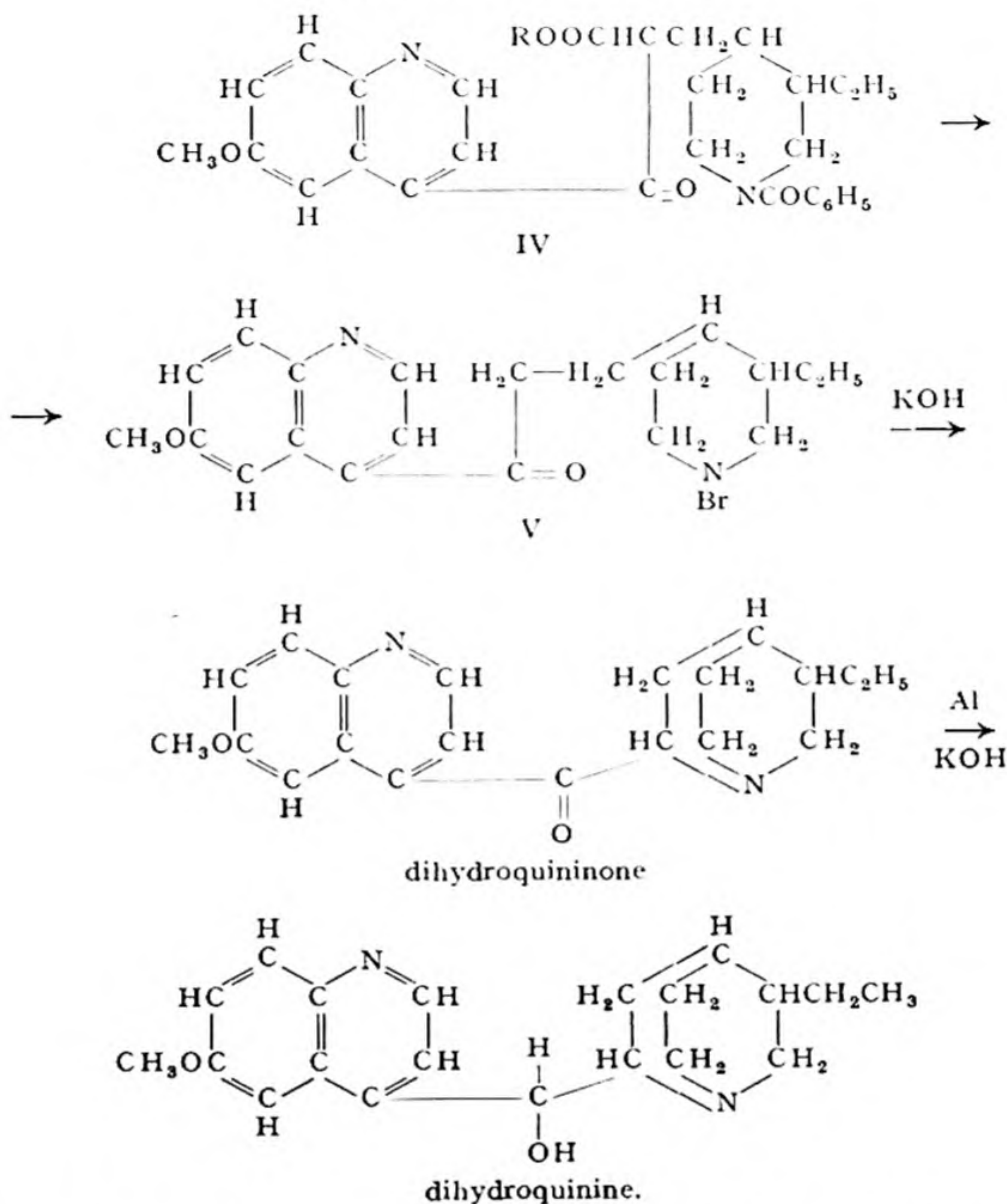
Structure of quinine. This base is to be regarded as the methoxy derivative of cinchonine. The methoxyl group is situated on carbon atom 6', *i.e.* in the *para*-position with respect to the nitrogen atom in the quinoline nucleus (see I). The presence of a vinyl group in quinine is proved in the same way as in cinchonine:



I. quinine

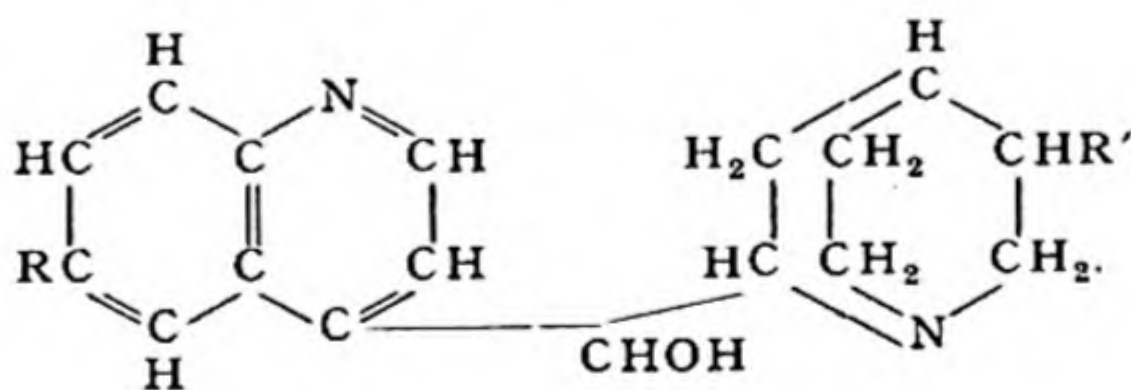


II quinone.



Quinine has been synthesised by WOODWARD and DOERING (1945); a description of this synthesis would take us too far however.

RABE has given the following general formula for the cinchona alkaloids:



In cinchonine and cinchonidine R is H and R' is $-\text{CH}=\text{CH}_2$. In quinine and quinidine R is OCH_3 and R' again $-\text{CH}=\text{CH}_2$. In the dihydro-bases R' is $-\text{CH}_2\text{CH}_3$.

Cinchonidine $\text{C}_{19}\text{H}_{22}\text{ON}_2$, a stereo-isomer of cinchonine, melts at 204° ; $[\alpha]_D = -178^\circ$.

Dihydrocinchonine $\text{C}_{19}\text{H}_{24}\text{ON}_2$, with m.p. 267° and $[\alpha]_D = 204^\circ$ and *dihydrocinchonidine*, $\text{C}_{19}\text{H}_{24}\text{ON}_2$, with m.p. 232° and $[\alpha]_D = -96^\circ$, both occur in very small quantities in cinchona bark.

Quinidine $\text{C}_{20}\text{H}_{24}\text{O}_2\text{N}_2$, a stereo-isomer of quinine melting at 173° , $[\alpha]_D = 324^\circ$, also occurs in small quantities in cinchona bark.

Dihydroquinine $C_{20}H_{26}O_2N_2 \cdot 2H_2O$ occurs in the bark of *cinchona ledgeriana*; it melts at 173.5° , $[\alpha]_D = -142^\circ$ (in alcohol) and possesses sufficient febrifugal properties to make it a useful drug.

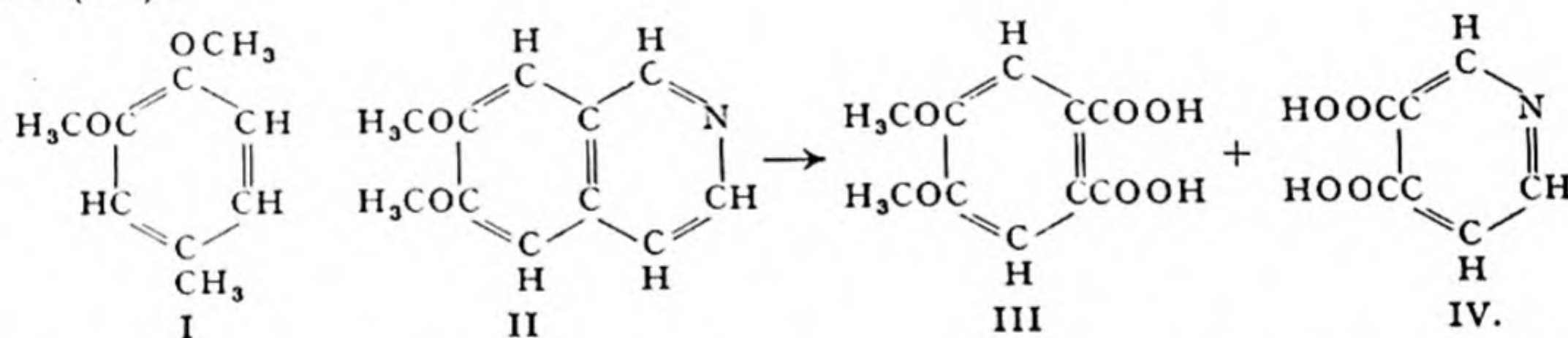
Dihydroquinidine $C_{20}H_{26}O_2N_2 \cdot 2.5H_2O$ occurs in cinchona bark and in unpurified quinidine; it melts at 169.5° and has $[\alpha]_D^{15} = 299^\circ$.

Alkaloids with an isoquinoline ring

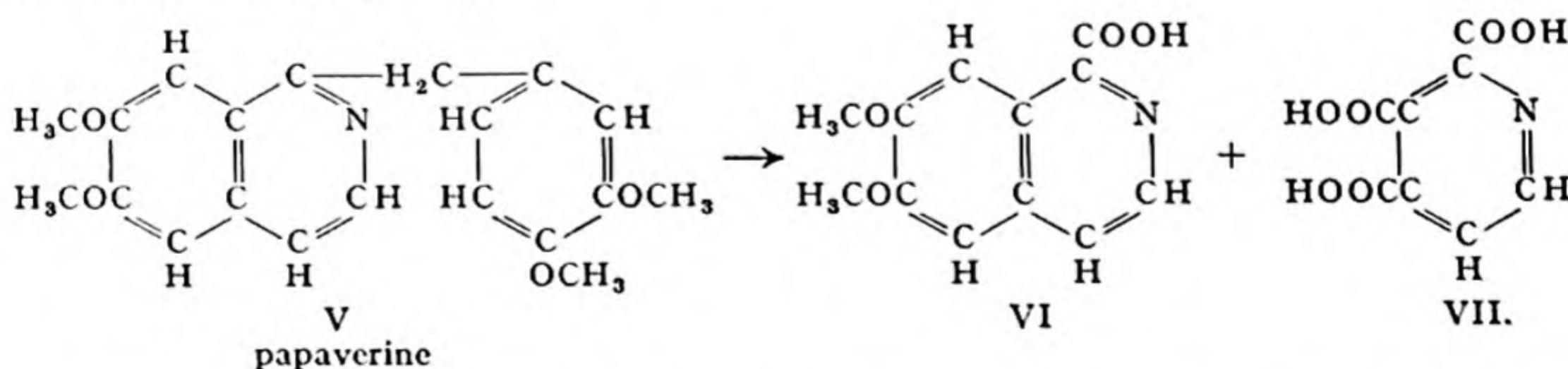
361. This class includes papaverine, laudanosine and narcotine, all of which occur in opium and which have been identified as benzyloisoquinoline derivatives.

Papaverine $C_{20}H_{21}O_4N$ was isolated from opium in 1848 (MERCK). It melts at 147° , is optically inactive, is very sparingly soluble in water and very readily soluble in chloroform. It is similar to morphine and codeine (**362**) in physiological action; it acts as a narcotic.

Structure. Papaverine has the properties of a tertiary base. On fusion with alkali it gives 3,4-dimethoxytoluene (homoveratrole) (I) and dimethoxyisoquinoline (II). The structure of the latter follows from its oxidation to 4,5-dimethoxyphthalic acid (meta-hemipinic acid) (III) and cinchomeronic acid (IV):

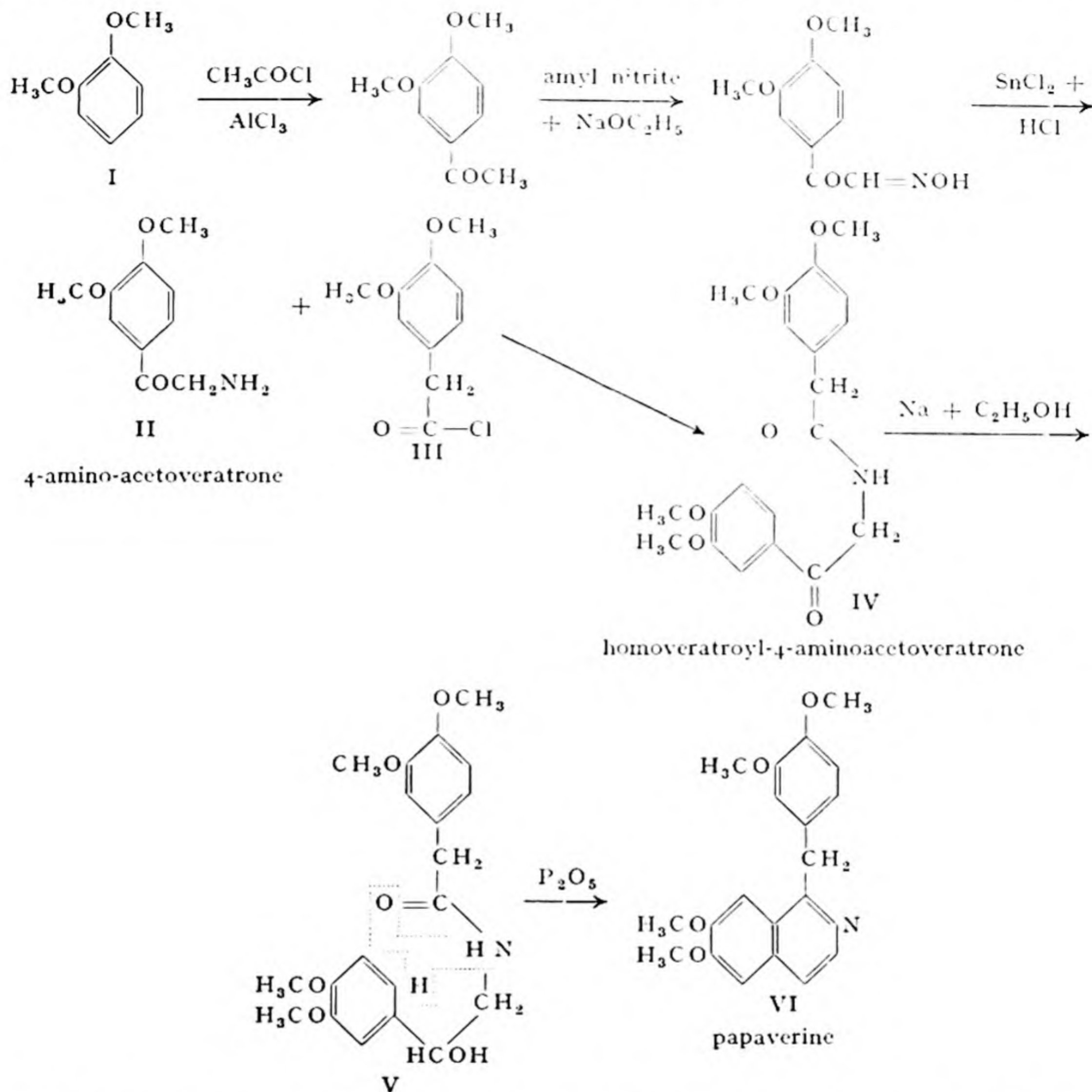


When papaverine (V) is oxidised with potassium permanganate, amongst other oxidation products there are produced 6,7-dimethoxy-isoquinoline 1-carboxylic acid (VI) and pyridine 2,3,4-tricarboxylic acid (α -carbocinchomeronic acid) (VII):



From this it follows that the dimethoxybenzyl group must be attached to the 1-position in the isoquinoline-ring. The formula set out by GOLDSCHMIDT (V) has been confirmed by a synthesis of PICTET and GAMS.

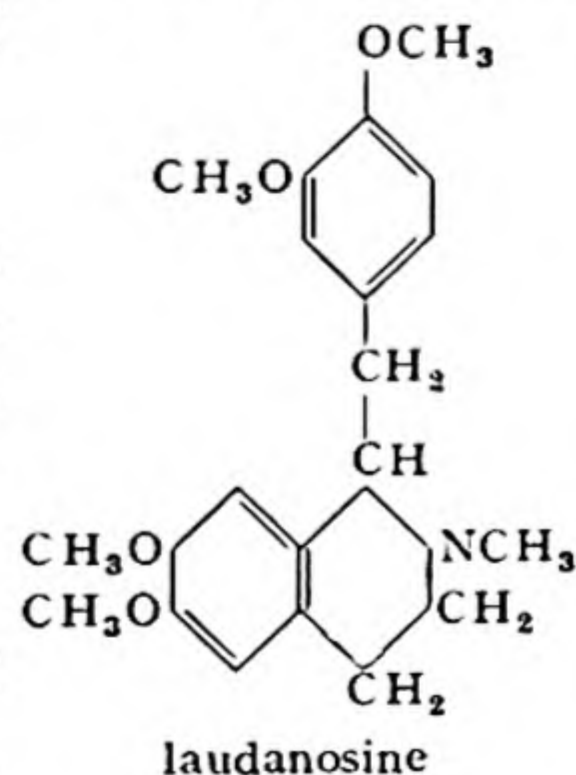
Veratrole or *o*-dimethoxybenzene (I) is first of all converted into 4-aminoacetoveratrone (II) as follows:



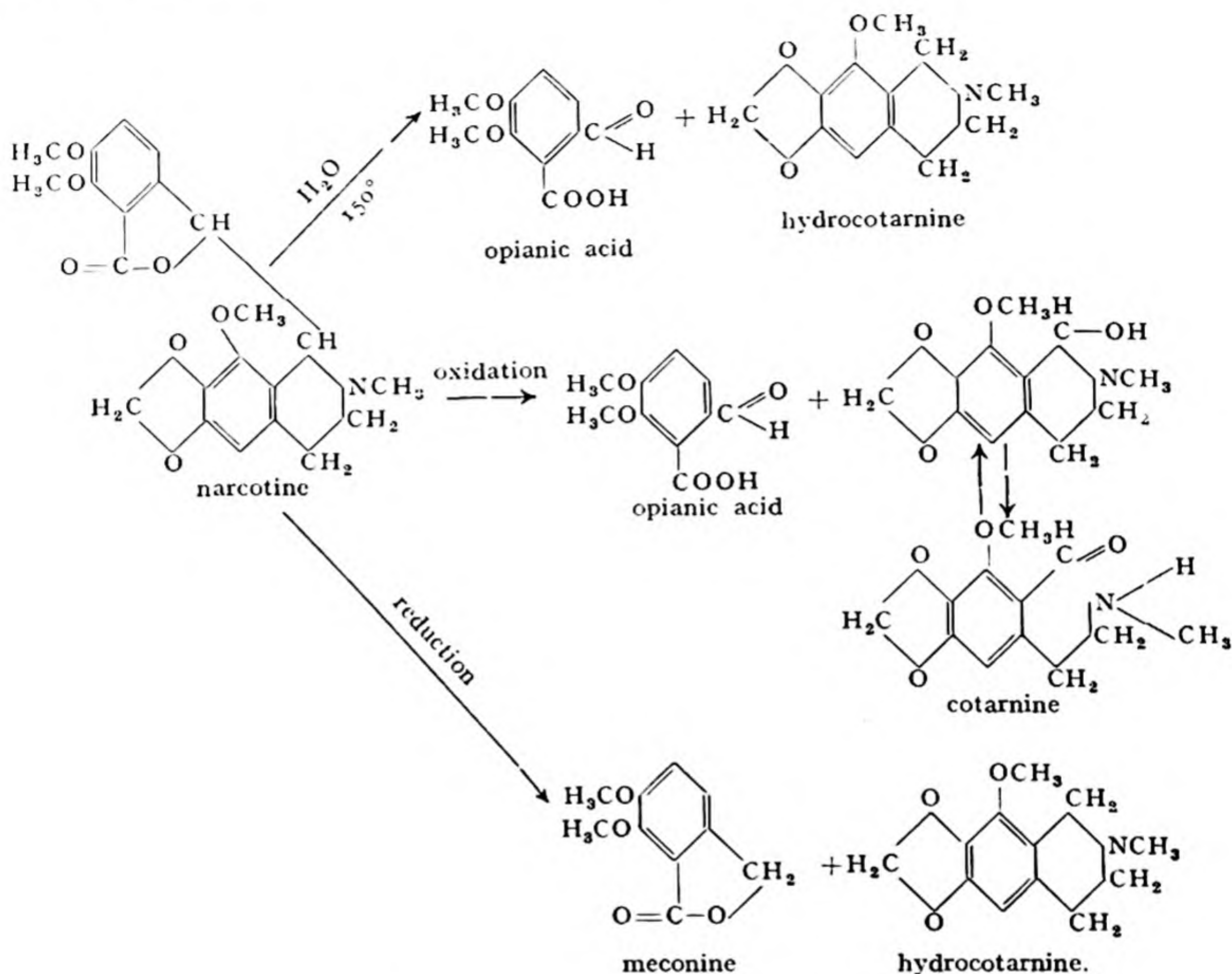
When **II** is treated with *homoveratroyl chloride* (**III**), *4-homoveratroylaminoacetoveratrone* (**IV**) is produced, which is reduced to the corresponding alcohol **V** by sodium and alcohol. By boiling a solution of **V** in xylene with phosphorus pentoxide ring-closure occurs with the formation of papaverine (**VI**).

Laudanosine $\text{C}_{21}\text{H}_{27}\text{O}_4\text{N}$ occurs in small amounts in opium. It is a derivative of papaverine being the N-methyltetrahydro-derivative. Its synthesis has been described by PICTET. It melts at 89° ; $[\alpha]_D = 103^\circ$ (in alcohol). It is more poisonous than papaverine.

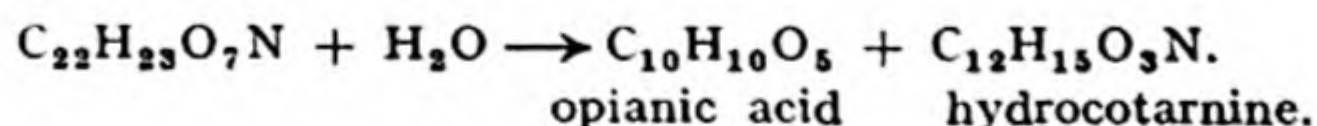
Narcotine $\text{C}_{22}\text{H}_{23}\text{O}_7\text{N}$ is one of the chief alkaloids of opium in which it occurs to the extent of about 10 %.



It was discovered by ROBIQUET in 1817; it melts at 176° , $[\alpha]_D = -198^\circ$ (in chloroform). In physiological action it resembles morphine (362) but is much less toxic.



Structure. Narcotine is a tertiary base and contains three methoxyl groups. It can be broken down in various ways. By heating with water to about 150° , *opianic acid* and *hydrocotarnine*, which also occurs in opium, are produced:



On oxidation, opianic acid and *cotarnine* are produced, while reduction gives *meconine* and hydrocotarnine. The narcotine molecule contains a partially hydrogenated and substituted isoquinoline ring, which is attached to a substituted benzyl group.

The structures of all these fission products have been proved by synthesis. It is beyond the scope of this book however, to discuss these in detail. Cotarnine melts at 133° and is used in medicine especially in gynaecology.

Phenanthrene alkaloids

362. These also occur in opium, the dried down, milky juice from the seed boxes of *papaver somniferum* etc., which is used in Asia on a large scale as a narcotic and a luxury article for producing stupor. About twenty five different alkaloids have been isolated from opium, namely, the *phenanthrene alkaloids* (morphine, codeine and thebaine), the isoquinoline bases (**339**) already discussed, and the *cryptonine alkaloids* to which belong *cryptopine* $C_{21}H_{23}O_5N$ and *protopine* $C_{20}H_{19}O_5N$.

Morphine was isolated from opium in 1814 by SEGUIN and by SERTÜRNER. The latter investigator characterised it as the first example of a vegetable base (1805).

The composition $C_{17}H_{19}O_3N$ was established by LAURENT (1847). Morphine melts at 254° ; $[\alpha]_D = -131^\circ$ in methanol. It gives well defined, crystalline salts with one equivalent of acid, e.g. the sulphate $(C_{17}H_{19}O_3N)_2H_2SO_4 \cdot 5H_2O$, and the hydrochloride $C_{17}H_{19}O_3N \cdot HCl \cdot 3H_2O$, both of which are soluble in water. Morphine is moderately soluble in water, very sparingly soluble in cold alcohol and more soluble in chloroform. It tastes bitter and has an anaesthetic action on the central nervous system; it causes sleep and is used in medicine as an anodyne.

Codeine $C_{18}H_{21}O_3N$ melts at 155° , $[\alpha]_D = -138^\circ$ in alcohol, is sparingly soluble in water and readily soluble in alcohol and chloroform. It is a moderately strong mono-acid base; the aqueous solution reacts neutral to litmus. Codeine has a bitter taste; its pharmacological action is similar to but weaker than that of morphine. It is less poisonous also than morphine.

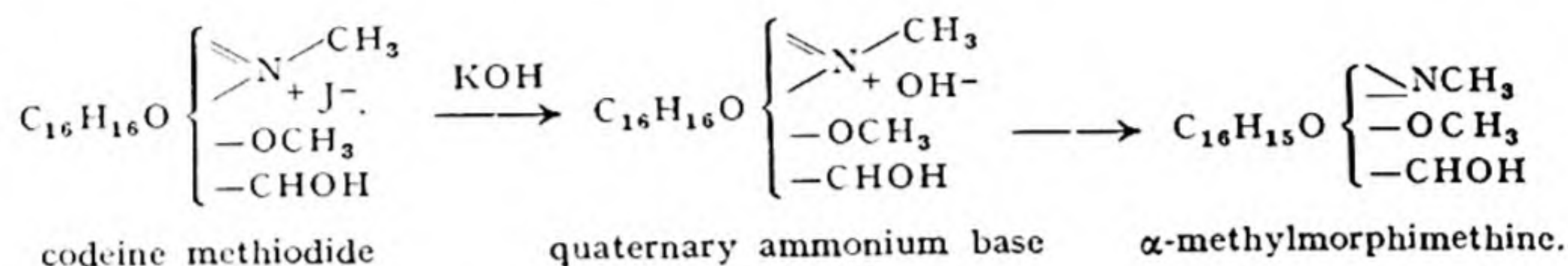
Colour reactions for morphine and codeine. Morphine gives a green colour with a solution of potassium bichromate in sulphuric acid and an orange-red colouration with concentrated nitric acid. A solution of a morphine salt gives a blue colour with a neutral solution of ferric chloride, which disappears on the addition of acid. Codeine does not give the ferric chloride reaction and gives a yellow product with nitric acid.

Structure of morphine and codeine. This has been the subject of some very difficult investigations which have been carried out right up to recent times (VONGERICHTEN, KNORR, PSCHORR, R. ROBINSON, etc.), only the main points can be touched on here.

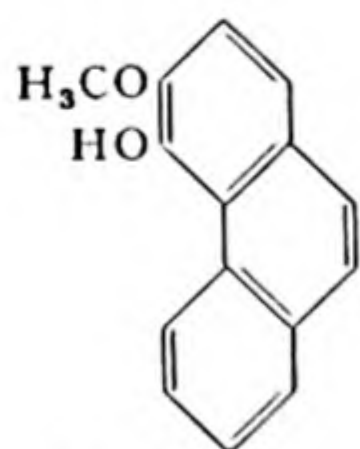
Morphine is a tertiary base. Of the three oxygen atoms, one is present as a phenolic hydroxyl group; this is responsible for the solubility of morphine in dilute alkalis. In codeine this phenolic hydroxyl group is replaced by a methoxyl group so that codeine is a mono-methyl ether of morphine and can be prepared from the latter by methylation. Codeine $C_{18}H_{21}O_3N$ can be converted by oxidation into *codeinone* $C_{18}H_{19}O_3N$, a compound, which

gives an oxime with hydroxylamine and therefore contains a ketone group. From this it follows that a secondary alcohol group is present in codeine, which can be represented as $C_{16}H_{16}O \begin{cases} \text{>N} \\ -OCH_3 \\ -CHOH \end{cases}$ and morphine as $C_{16}H_{16}O \begin{cases} \text{>N} \\ -OH \\ -CHOH \end{cases}$.

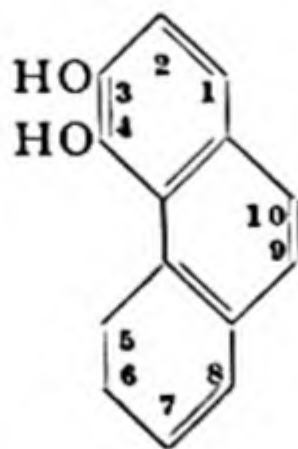
The third oxygen atom is combined as an ether as is shown from the examination of the degradation products from both the alkaloids. When methyl iodide is added on to codeine and the quaternary salt is warmed with potassium hydroxide solution, water is split off and α -methyilmorphimethine is produced:



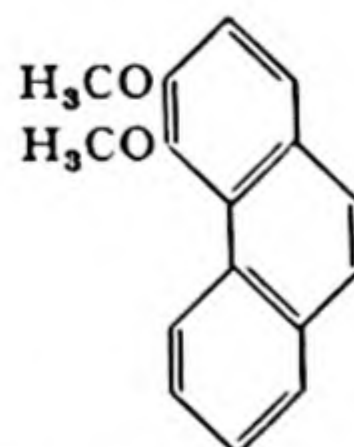
This compound is decomposed by warming with acetic anhydride giving *dimethylaminoethanol* $(CH_3)_2NCH_2CH_2OH$ and *morphol mono-methyl ether*, which is identical with *3-methoxy-4-hydroxyphenanthrene*. By methylating the latter, morphol dimethyl ether is obtained, which is identical with *3,4-dimethoxyphenanthrene* obtained synthetically (PSCHORR, 284). From this it follows, that the molecules of codeine and morphine contain a phenanthrene skeleton. With regard to the dimethylaminoethanol, which is formed as a fission product, one methyl group is derived from the methyl iodide and the other must therefore have been combined to a nitrogen atom in codeine, so that codeine and morphine must contain the group $-CH_2CH_2NCH_3$, which must be attached to the phenanthrene-ring.



morphol mono-methyl ether



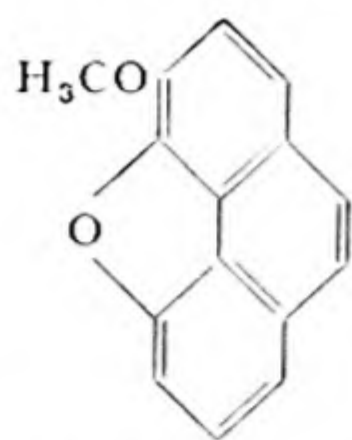
morphol



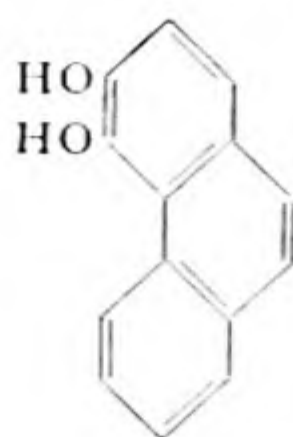
morphol dimethyl ether.

When the degradation of α -methyilmorphimethine is carried out in another way, *morphenol methyl ether* is produced. This compound, which contains a phenol group and an ether-linked oxygen atom, can be converted into morphol by eliminating the methyl group and reducing the product.

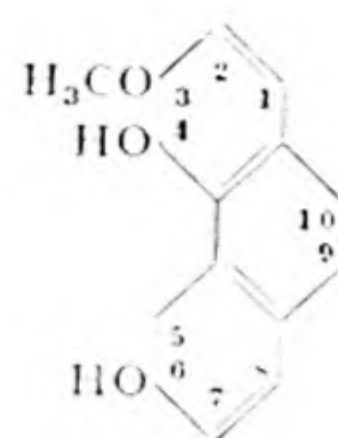
When codeinone is heated with acetic anhydride, *methylaminoethanol* $CH_3NHCH_2CH_2OH$ is produced along with the diacetyl derivative of



morphenol methyl ether



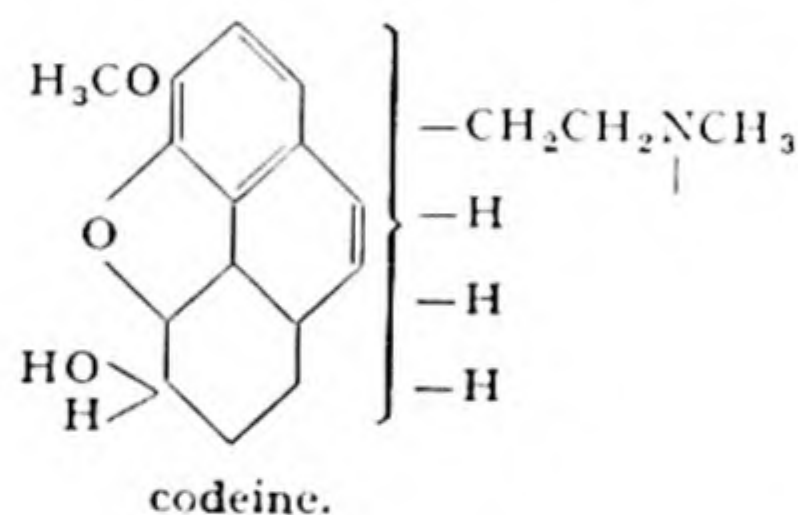
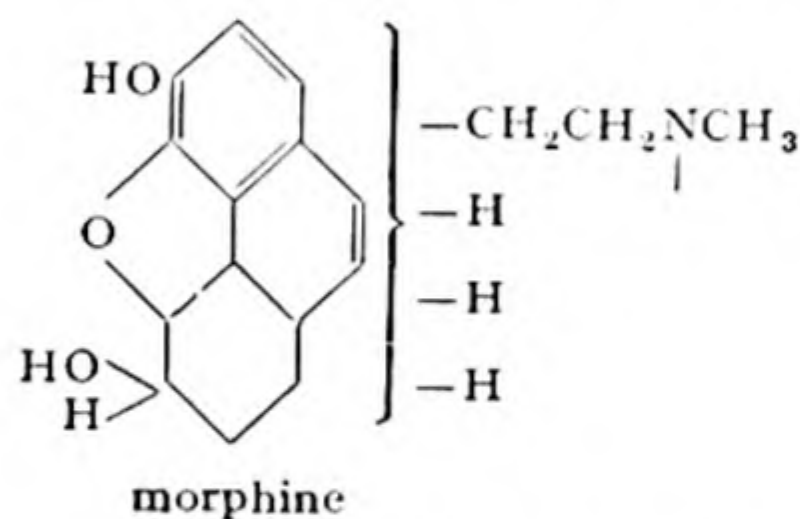
morphol



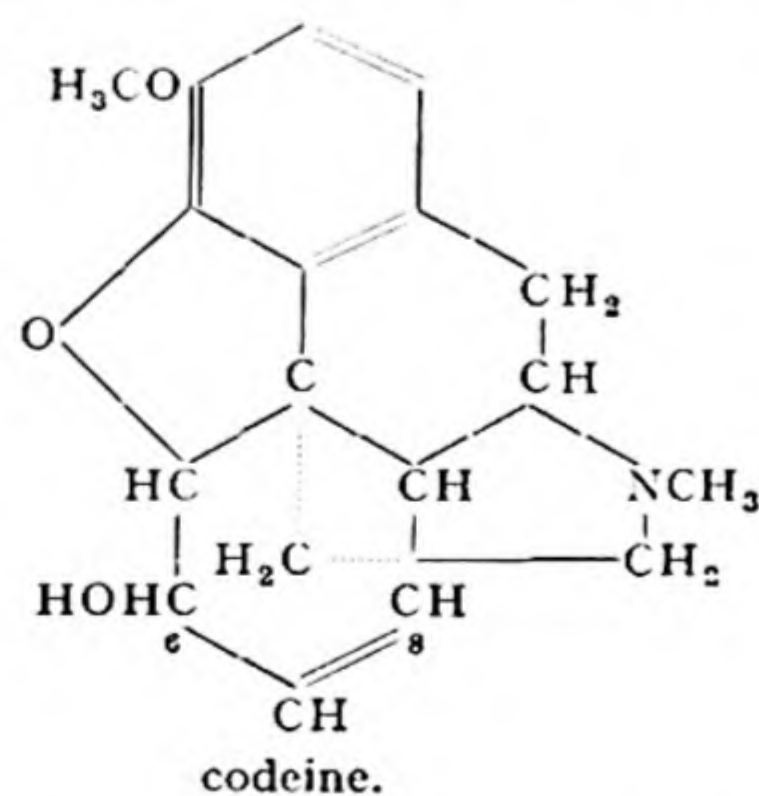
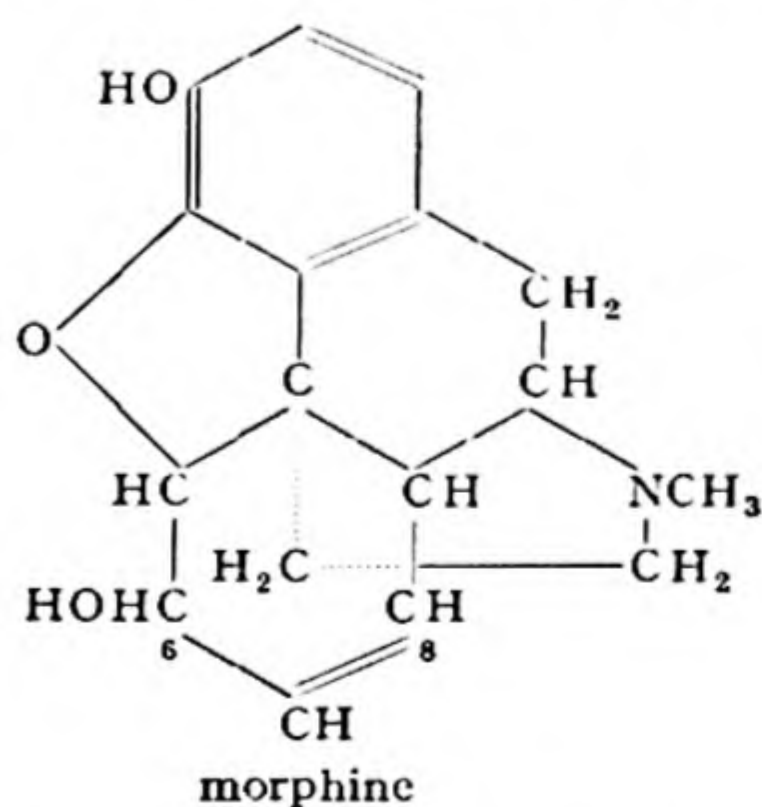
3-methoxy-4,6-dihydroxyphenanthrene

3-methoxy-4,6-dihydroxyphenanthrene, the structure of which has been established by synthesis. The formation of this phenanthrene derivative can be explained by assuming that codeinone reacts in a tautomeric form in which the group $\text{—CO—CH}_2\text{—}$ passes over into the grouping —COH=CH— . In this way the position of the keto-group in codeinone is established and therefore also the position of the >CHOH -group in morphine and codeine.

Morphine and codeine can now be represented by the following formulae:



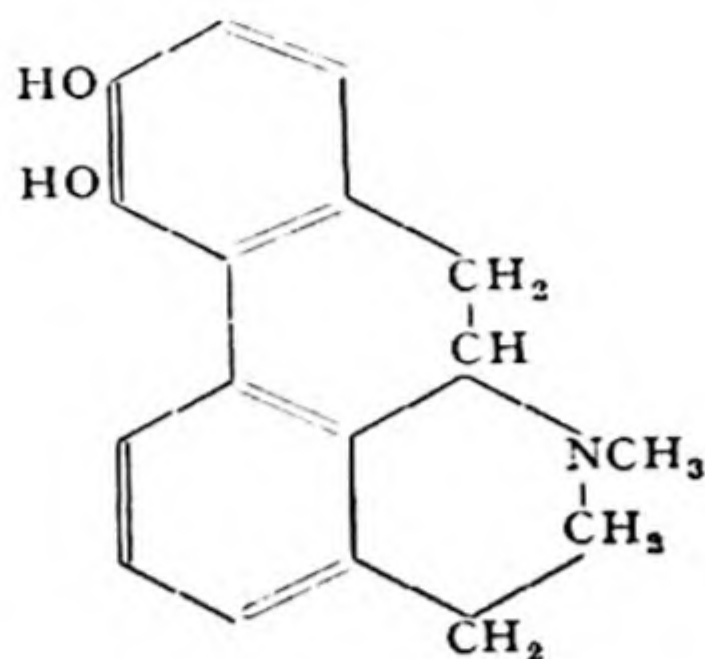
The mode of attachment of the nitrogenous portion of the molecule was established only recently. It would, however, take us too far to deduce the structure of this ring-system and it must suffice to state only that the annexed formula, suggested by Sir ROBERT ROBINSON, best represents the facts:



Some isomers of morphine and codeine are known. α -*Isomorphine* is a stereo-isomer of morphine. α -*Isocodeine* is a stereo-isomer of codeine. Both of these iso-bases differ from their isomer in the different position of the OH-group and the hydrogen atom on carbon atom 6.

By the action of dehydrating agents on morphine there is produced *apomorphine* $C_{17}H_{17}O_2N$, which may be regarded both as a phenanthrene derivative and as an isoquinoline derivative.

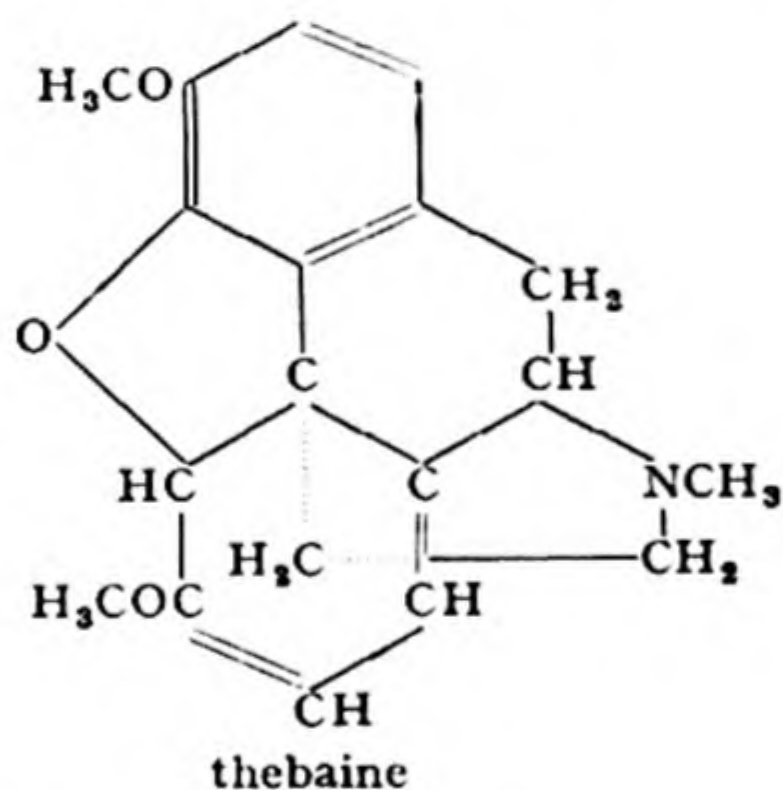
Apomorphine has a stimulating action on the central nervous system and causes vomiting.



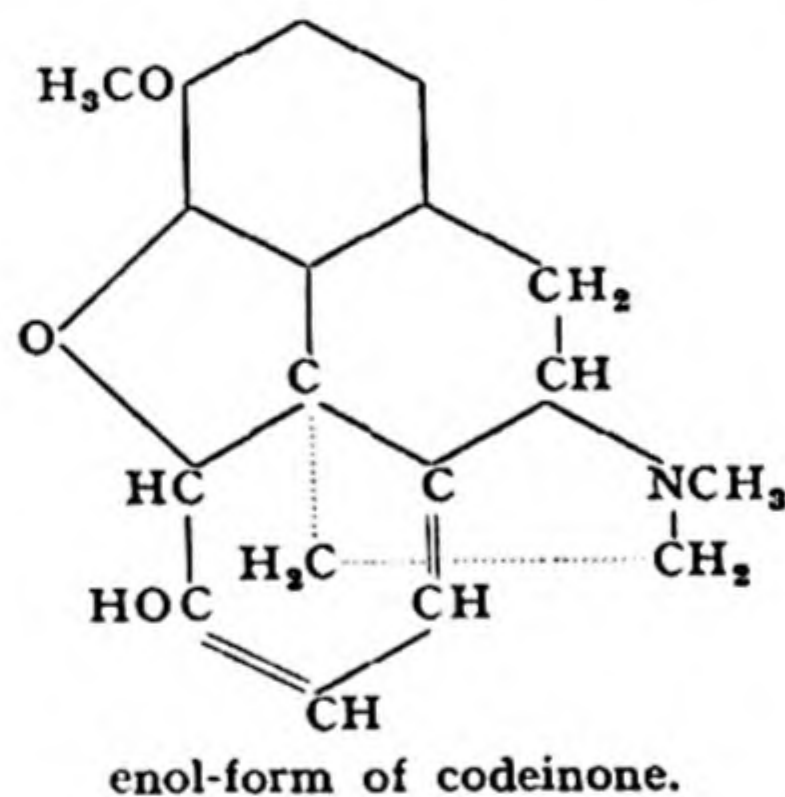
apomorphine.

Thebaine $C_{19}H_{21}O_3N$, was isolated in 1835 by PELLETIER from opium, in which it occurs in small amounts. It melts at 103° , $[\alpha]_D^{15} = -218^\circ$ in alcohol. It has a powerful toxic action and is not used to any great extent in medicine.

By the action of dilute sulphuric acid, thebaine is converted into methyl alcohol and codeinone; thebaine is the methyl ether of the enol form of codeinone. (Schöpf)



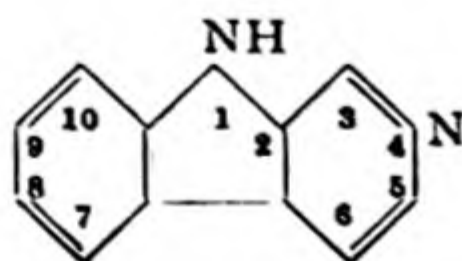
thebaine



enol-form of codeinone.

Carboline alkaloids

363. Those vegetable bases containing a *carboline* ring-system belong to this class of alkaloids. This system consists of an indole nucleus (315) condensed in the 2-3 position with a pyridine ring in the 3 and 4 positions. Some alkaloids are simple derivatives of carboline like the harman alkaloids. Some, however, like yohimbine, are more complex derivatives:

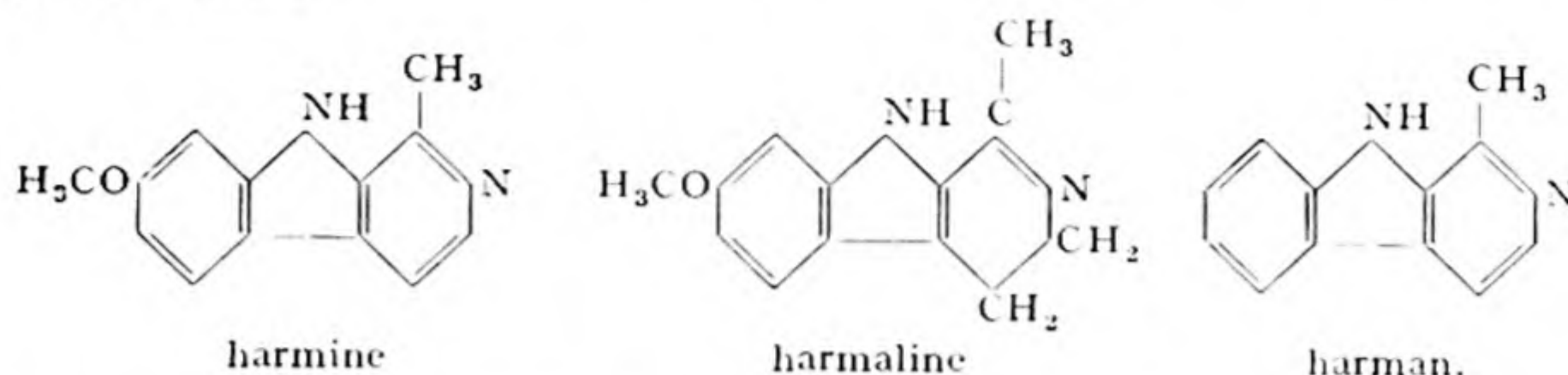


carboline.

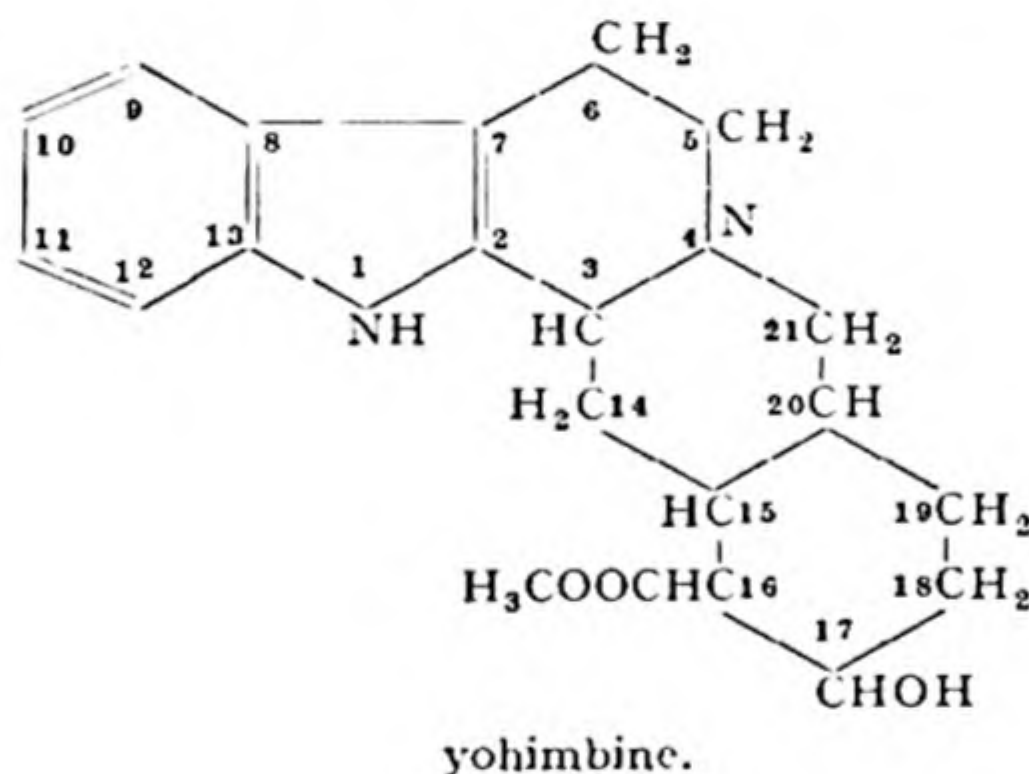
Harman alkaloids. These alkaloids are distributed fairly widely in the vegetable

kingdom, *e.g.* in *peganum karmala*, an American lianas. The structure of these alkaloids has been elucidated mainly by PERKIN and ROBINSON.

Harmine $C_{13}H_{12}ON_2$ melts at 261° and is optically inactive. Its structure, like that of *harmaline* $C_{13}H_{14}ON_2$ (m.p. 240°) and of *harman* $C_{12}H_{10}N_2$ (m.p. 238°), has been proved by synthesis:



Yohimbine or *quebrachine* $C_{21}H_{26}O_3N_2$ occurs in the leaves and bark of *coryanthe yohimbe*, the yohimbe tree which grows in Central Africa. It dilates the blood vessels and finds a use in veterinary practice. Its structure has been established by the researches of BARGER and SCHOLZ, WIBAUT and MENDLIK, JULIAN and others. Yohimbine contains a $-\text{COOCH}_3$ -group and an alcoholic hydroxyl group. Dehydrogenation of yohimbine with selenium gives *yobyryne* $C_{19}H_{16}N_2$, *ketoyobyryne* $C_{20}H_{16}ON_2$ and *tetrahydroyobyryne* $C_{19}H_{20}N_2$. When fused with alkali, ketoyobyryne gives 2,3-dimethylbenzoic acid and harman. Other degradation products are hemimellitic acid $C_6H_3(\text{COOH})_3$ — (1,2,3), *m*-toluic acid and berberonic acid or pyridine 1,3,4-tricarboxylic acid.



Strychnos alkaloids

36.4 A number of alkaloids, of which *strychnine* and *brucine* are the most important, occur in the seeds of *strychnos nux vomica* (St. Ignatius' beans) and in other kinds of *strychnos*; both alkaloids are very poisonous and cause death with violent spasms (*i.e.* contractions of the muscle tissues). Strychnine and brucine were discovered in 1817 and 1819, respectively, by PELLETIER and CAVENTOU.

Strychnine $C_{21}H_{22}O_2N_2$ is a crystalline compound melting with decomposition between 268° and 290° , $[\alpha]_D = -110^\circ$ (in 80 % alcohol); it is practically insoluble in water. A characteristic reaction for strychnine takes place when the substance has concentrated sulphuric acid poured upon it and then a crystal of potassium bichromate is added; a blue colouration is produced, which passes through violet and red to green.

The structure of *strychnine* is at present best represented by Fig. 67 (Sir ROBERT ROBINSON), which finds confirmation in a complete X-ray analysis of crystals of strychnine sulphate and selenate (BIJVOET, BOKHOVEN, SCHONE, 1948).

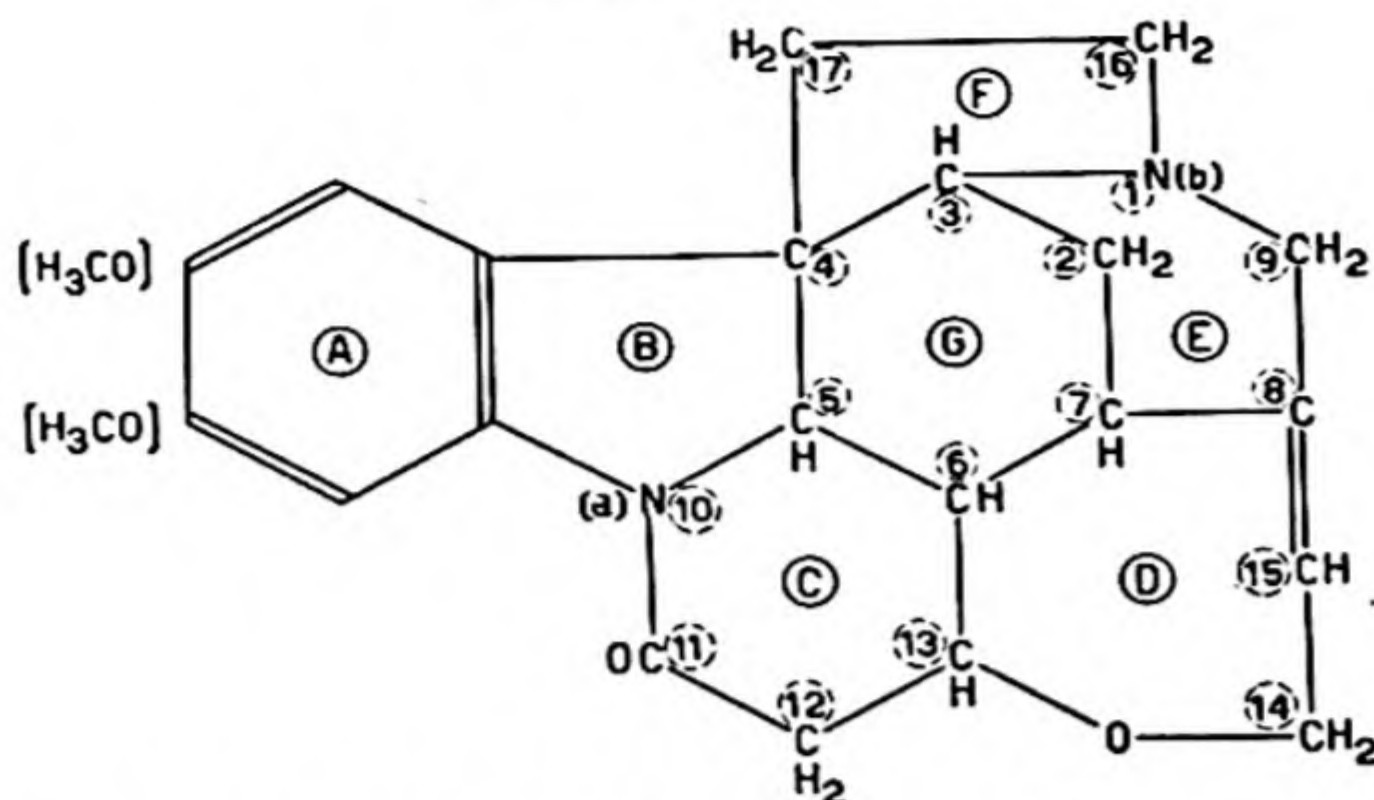


Fig. 67. Structure of strychnine according to Sir ROBERT ROBINSON (with two OCH_3 -groups = brucine).

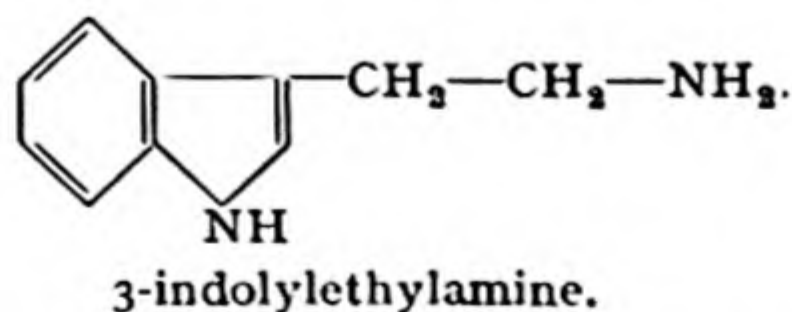
This has been deduced from the results of tedious and very difficult researches for which we have to thank HANSEN, TAFEL and later more especially LEUCHS, ROBINSON and WIELAND. In this place it is only possible to give a few explanations with regard to this structural formula. From the composition of strychnine salts *e.g.* $(\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_2)\text{HNO}_3$ it follows that only one of the two nitrogen atoms has basic properties; this is the tertiary nitrogen atom (b). The other nitrogen atom (a) is in a lactam group (194). This lactam ring C can be opened by hydrolysis whereby an iminocarboxylic acid $(\text{C}_{20}\text{H}_{22}\text{ON})(\text{NH})\text{COOH}$ is produced; strychnine can be re-formed from this compound by elimination of water. By electrolytic reduction of strychnine there is produced *strychnidine* $\text{C}_{21}\text{H}_{24}\text{ON}_2$, in which the group $>\text{CO}$ is reduced to $>\text{CH}_2$. Strychnidine gives salts with two equivalents of acid *e.g.* $\text{C}_{21}\text{H}_{24}\text{ON}_2 \cdot 2\text{HCl}$.

By very powerful reduction, an oxygen-free base $\text{C}_{21}\text{H}_{28}\text{N}_2$, is finally obtained from strychnine; the second oxygen atom in strychnine is present in the form of an ether bond.

By careful catalytic reduction of strychnine or strychnidine, two atoms of hydrogen are taken up, which indicates the presence of an easily reducible $>\text{C}=\text{C}<$ bond; this is assumed to be between C (15) and C (8).

On heating a methyl derivative of strychnine with soda-lime, there is produced amongst other things, carbazole (317), derived from the ring system A, B, G. By the action of concentrated nitric acid there is eventually produced, via numerous intermediate products, a dinitro-derivative of isatin (316) derived from ring systems A and B.

By degrading strychnine in alkaline media there are produced a number of substances including indole, 3-ethylindole and 3-indolyethylamine (tryptamine, compare tryptophan 199), derived from rings A and B, carbon atoms 3 and 2 and nitrogen atom 1 (b):



Brucine $\text{C}_{23}\text{H}_{26}\text{O}_4\text{N}_2$, is a dimethoxy-derivative of strychnine. It melts at 178° , $[\alpha]_D = -80^\circ$ in absolute alcohol.

Since strychnine and brucine are easily obtained, these alkaloids are used for destroying noxious rodents.

APPENDIX

HINTS ON SEARCHING THE LITERATURE ON ORGANIC CHEMISTRY

Searching the literature on organic compounds is made possible by the use of reference journals, literature indexes and encyclopaedic handbooks.

The literature on chemical subjects is abstracted practically completely in three journals, viz. in *Chemical Abstracts* (America), the *Chemisches Zentralblatt* (Germany) and *British Chemical Abstracts*.

These journals contain abstracts of articles appearing in the various periodicals and usually give a complete account of the experimental data.

Chemical Abstracts (published by the American Chemical Society) begin in 1907 and appear twice monthly. In each number there is an author index. Once each year there appears an author index, a formula index and a subject index dealing with the articles abstracted the previous year, and every ten years, a collective index appears, in which subjects and authors appearing during the preceding ten years are arranged alphabetically and the subjects very briefly abstracted.

The *Chemisches Zentralblatt* (originally published by the German Chemical Society) begins in 1897 as a continuation of the *Chemische Jahresberichte*, which first appeared in 1847.

The *Zentralblatt* appears weekly. In each number there is an author index; twice annually an author and a patent index are published and subject and formula indexes appear annually. Every five years there appears a collective index containing authors' names and the names and the formulae of compounds mentioned during this period.

In the years after the second world-war, the *Zentralblatt* has appeared temporarily in two different editions, one from the Russian zone and one from the American zone of Germany. Both editions carry the same volume number but the contents are not identical. The publishing of the journal from the American zone has been suspended from January 1st, 1950 and the edition from the Russian zone is being published exactly as before the war.

British Chemical Abstracts have been published by the Chemical Society of London from 1871 until 1926, when abstracting was taken over

by the Bureau of Abstracts. British Abstracts are published in sections, which may be purchased separately. The coverage is less thorough than that of the American and German abstracts, though some journals are covered which are not abstracted by the other two. The subject indexing compares unfavourably with the German and American abstracts and there is no regular issue of collective indexes. British Abstracts are widely used in the British Isles.

In RICHTER's *Lexicon der Kohlenstoffverbindungen* are to be found the empirical formulae of all compounds known before the end of 1910, arranged in order of increasing number of carbon atoms. The formulae of compounds from 1911–1921 inclusively, are to be found in STELZNER's *Literatur-Register der Organischen Chemie* and after 1921 they are to be found in the formula-indexes of the *Chemisches Zentralblatt*.

In RICHTER, after the formula of a compound, reference are made to the description of it in BEILSTEIN's Handbook (abbreviated to B) discussed below. In addition, for each compound, RICHTER mentions the most important original literature. In STELZNER's indexes, with each particular compound is given all the literature which has appeared on this compound during the year under consideration. The same applies to the *Zentralblatt* indexes.

Below is given a brief summary of the classification of BEILSTEIN's *Handbuch der Organischen Chemie*.

In the fourth edition of this handbook the literature to 1910 is collected together in 27 volumes or parts of the *Hauptwerk*; the first *Ergänzungswerk*, consisting of 15 volumes, deals with the literature to 1920; the second *Ergänzungswerk*, about half of which is now ready, continues to 1930. Subject and formula indexes have appeared for the *Hauptwerk* and first *Ergänzungswerk* together. Further, there are two volumes which are a combination of the *Hauptwerk* and the first *Ergänzungswerk*, viz. a volume on natural products (including rubber and carotinoids) and a volume on carbohydrates.

In the contents list in each volume of BEILSTEIN, there is given the various classes of compounds dealt with in that particular volume, so that in searching for many compounds it is sufficient to consult the contents. However, numerous compounds are known, which may be regarded as belonging to different classes, because they are derivatives of two or more other compounds. In general, such compounds are classified in the latest position coming up for consideration. The system followed in BEILSTEIN can be studied in a booklet belonging to the main work, *Ein Leitfaden für die Benutzung von Beilsteins Handbuch der Organischen Chemie*. Each compound is set down under a definite numerical system; the appropriate

system-numbers are printed on each volume. For further particulars reference should be made to the "Leitfaden" just mentioned.

When once the required compound has been found in BEILSTEIN, all particulars and therefore the most important literature references to this particular compound, will be mentioned, so that the original publication up to 1930 can always be found from BEILSTEIN.

For the literature on compounds described after 1930, a search must be made of the indexes of the Zentralblatt or, Chemical Abstracts or in ELSEVIER's *Encyclopaedia of Organic Chemistry*.

The latter handbook will appear in 18 volumes, some of which will comprise several parts; the whole will be completed by two volumes of general indexes. The system of indexing differs from that of BEILSTEIN; the starting point is not the functional groupings present in the compound, but the carbon skeleton, so that all derivatives of the same ringsystem, for example, are found together in one volume.

So far the following volumes have been published: volume 14, dealing with compounds belonging to isocyclic ring-systems with four or more condensed rings; volume 13 with ring-systems with three condensed rings; volume 12 A with bicyclic isocyclic compounds except naphthalene; four parts of volume 12 B dealing respectively with naphthalene and its halogeno-, nitrogen, hydroxy- and keto-compounds. The four parts deal respectively with the literature up to 1936, 1936, 1941 and 1944, inclusively. Supplementary volumes to each of those already published are to be issued at ten yearly intervals and the first of these, a supplement to volume 14 covering the literature from 1937 to 1946, has already appeared.

The *Dictionary of Organic Compounds* edited by HEILBRON, is a book which can facilitate the search of the literature. This book lists a large number of compounds arranged alphabetically and gives for each one, the formula, its physical constants and the original literature where the compound is first described. This dictionary, however, is not complete as regards either the substances described or the literature on the compounds mentioned.

If now it is desired to look up particular methods used in organic chemistry, all kinds of preparative recipes and detailed literature references are to be found in HOUBEN-WEYL, *Die Methoden der Organischen Chemie*. The book is, however, somewhat out of date.

The literature on new methods for the synthesis of organic compounds is indexed in THEILHEIMER's *Synthetische Methoden der Organischen Chemie*; improvements of well known and tested older methods, which occur widely distributed over all kinds of technical periodicals, are also mentioned.

The literature for the years 1942-1944 is abstracted in the first volume, that for 1945-1946 in the second, that for 1946-1947 and part of 1948

in volume 3 and that for 1947-1948 and part of 1949 in volume 4. Volume 3 contains an index to volumes 1-3. An English translation of volumes 1 and 2 has appeared.

Excellent recipes for the preparation of numerous organic compounds, which have been carefully checked in two or three independent laboratories, are to be found in *Organic Synthesis*, "An annual publication of satisfactory methods for the preparation of organic chemicals", 30 volumes of which have appeared up to 1950.

Organic Reactions by ADAMS, in the production of which many well known American organic chemists collaborate, sets out from the idea, that in the applications of a particular method or reaction, it is desirable to know under what conditions the reaction takes place most satisfactorily. Each of the five volumes, which have so far appeared, is a collection of chapters, each devoted to one reaction or particular phase of a reaction under various possible methods of application. Each author has himself experimented with the method described. Tables complete the text with examples of compounds, which are either obtained by this method, or on which the method in question has been used.

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